NEWSLETTER

No. 2 - 2016

RSNN
Regulatory Science Netwerk Nederland

Dear Reader,
This is the second Regulatory Science Network Netherlands (RSNN) Newsletter. The RSNN, a network for experts from academia, government, the pharmaceutical industry, patient organisations, and others involved in regulatory activities related to drug development, aims to facilitate activities in the field of Regulatory Science in the Netherlands by stimulating dialogue and collaboration, and sharing information and methods. The RSNN is aligned with other European platforms active in the field.
The RSNN Newsletter informs participants and stakeholders of activities and developments in the discipline. This edition reports on Regulatory Science sessions held at the FIGON Dutch Medicines Days on October 3 2016, which focused on the regulatory aspects of orphan drug development and the search for new methods of scientific research in small patient groups.

REGULATORY SCIENCE MORNING SESSION:
HOW DOES REGULATORY SCIENCE DRIVE ORPHAN DRUG DEVELOPMENT?

Just Weemers (NVFG) welcomed more than 80 attendees and presented the day's agenda. The morning session focussed on how Regulatory Science can drive orphan drug development and the afternoon's more on clinical research, in particular the challenges of conducting research in small populations. Speakers from three different parties involved in orphan drug development were invited to share their experiences: regulators, the pharmaceutical industry, and academia; and as Just Weemers stated *"They'll all give you a different answer based on their different perspectives on orphan drug development"*.

The first speaker, **Prof Dr Bert Leufkens (Medicines Evaluation Board [MEB] /University Utrecht)**, introduced the theme of the morning session referring to a recent article by Marlene Heffner, one of the founders of orphan drug development.[1] The article gives a good picture of 20-30 years of orphan drug development, a success story that started in 1982 with the United States (US) Orphan Drug Act, the first such legislation in the world. As a result more than 500 drugs for rare diseases have been developed in the US.
In the European Union (EU) Orphan Drug legislation was developed in 1999. Although there are still challenges, such legislation has strongly stimulated the development of innovative drugs for rare diseases. An important issue for the MEB, especially with regard to Regulatory Science, is how to define a specific disease: in molecular, clinical, or genetic terms? →

SAVE THE DATE MEB REGULATORY SCIENCE DAY
'Generic Drugs in Society'
The Regulator's Dilemma
Date: Friday February 3rd, 2017 12.00 – 18.00 hrs
Further details: **https://english.cbg-meb.nl/latest/news/2016/12/23/meb-regulatory-science-day-2017**

CALL FOR AGENDA TOPICS - YOUR INPUT IS NEEDED!
One of the goals of the RSNN is to bring all stakeholders to the table, to stimulate open conversations, and support steps towards the changes needed in the regulatory process. RSNN 'S agenda is driven by developments in the life science area and needs your input. We therefore call for agenda items that you feel should be shared and discussed with colleagues in the field of regulatory science. Currently, biomarkers and precision medicine are topics we focus on, but we are sure that there are more. Please share your ideas and suggestions using the contact details at the end of this newsletter.

JOIN THE RSNN
The RSNN is an open network. You can join it by contacting Barbara van Veluw – Greebe (email: b.v.veluw@cbg-meb.nlb.v.veluw@cbg-meb.nlb.v.veluw@cbg-meb.nl), but also by becoming a member of our LinkedIn group. **https://www.linkedin.com/groups/8559430**

And by extension, how do we measure outcome? Which (bio)marker(s) can be used? And which study design is applicable and also feasible? Here Regulatory Science can make the difference between success and failure by evaluation of regulatory systems' ability to ensure patient safety, enhance public health, and stimulate innovation. Other key questions are: How much evidence is enough? How do we bring a new compound to the regulator for approval? Here Regulatory Governance and Regulatory Science meet and work together.

Mitochondrial Diseases

The next speaker, **Prof Dr Jan Smeitink (Khondrion BV),** presented a real life example of the Regulatory aspects of Orphan Drug Designation. Khondrion, founded by Jan Smeitink in 2012, is a company that focuses on the development of innovative therapies for inherited mitochondrial diseases, including Leigh Disease. Mitochondrial diseases are the result of inherited or spontaneous mutations in mitochondrial DNA or nuclear DNA. Such mutations lead to altered or failed mitochondrial-protein or ribonucleic-acid-molecule functionality. As a result, energy generation within the cell decreases. Cell injury and even cell death may follow. If this process is repeated throughout the body, whole systems begin to fail, and life itself may be severely compromised. The disease primarily affects children, but adult onset is becoming more common. Prevalence is approximately 1 in 10,000.[2]

In partnership with the Radboud Center for Mitochondrial Medicine, Khondrion has developed a new compound (KH176) to treat such patients. KH176 represents a novel class of mitochondrial-targeted compounds with proven efficacy for all mitochondrial diseases with an altered redox homeostasis, including MELAS and Leigh.

BOX 1: Mitochondrial disease: hard to keep up with!

"Mitochondrial diseases are by nature so complicated, and the developments in the mitochondrial medicine field are moving so fast, that for authorities it is almost impossible to have sufficient knowledge to rapidly change classical views regarding disease classifications and mechanisms in to more up to date concepts regarding granting Orphan Drug Designations" (Jan Smeitink 2016).

KH176 now has orphan drug designations from both the EMA and FDA. But one hurdle to overcome still in the EU is that the authorities grant Orphan Drug Designation to specific diseases, such as 'MELAS' and 'Leigh', and not disease groups like 'Oxphos disorders'. This is a challenge because classification of mitochondrial diseases on clinical, and/or biochemical, and/or genetic grounds is very complex, if not impossible [Box 1]. This knowledge gap leads to delays and increased costs in the Orphan Drug Designation procedure; changes should be made, to align with the US. "How to convince the EU authorities to change the system?" Jan Smeitink put this question to the audience which concluded that this is a problem of definition and lack of flexibility in the EU regulatory system.

Committee for Orphan Medicinal Products (COMP)

With the previous subject still in mind, Just Weemers introduced the next speaker **Dr Violeta Stoyanova-Beninska,** who is a member of the COMP. The COMP, a committee of the European Medicines Agency (EMA), is responsible for reviewing applications from people or companies seeking 'orphan-medicinal-product designation' for medicines to be developed for diagnosis, prevention or treatment of rare, life threatening or very serious diseases. In the EU, a disease is defined as rare if it affects fewer than 5 in 10,000 people across the EU.[3]

Between 2000 and September 2016, applications and designations have gradually increased to 1,733, but only 122 orphan medicinal products have received marketing authorisation. So orphan designation status does not guarantee that orphan medicinal products reach marketing authorization. Today, 10-15% of designated orphan medicinal products fail to re-confirm orphan status at the time of marketing authorization, in a few cases because the disease prevalence has increased above the threshold but mostly because of lack of data to support 'significant benefit'.

Just Weemers asked Violeta how the COMP can keep up with new techniques in drug development and anticipate the need for change. Violeta explained that according to the European Committee (EC), changing legislation is a very long process which the EC undertakes only if absolutely necessary, while a faster and more flexible option is to change the guidelines which help researchers to interpret legislation. She added that in recent developments, the COMP faces several challenges which members address through various lines of research. One

example is in defining the 'orphan condition', e.g., the use of classification systems, delineating haematological orphan conditions, 'subsets' as defined by the increasing knowledge of biomarkers, or 'umbrella terms' as in mitochondrial disease. Another line of research focuses on reviewing the animal models developed for rare disease and their appropriateness in drug development. This is where the RSSN comes in: trying to match the different worlds of drug development and legislation, and stimulating cooperation.

Expanded Access

In the next presentation, **Dr Eline Bunnik (Erasmus MC)** gave an excellent overview of a project aimed at analysing ethical issues in relation to 'expanded access' programs. In particular, the project tries to elucidate the physicians' role by mapping their experiences and decision-making processes: how do physicians decide if a patient is eligible for an investigational drug? What conditions lead them to pursue expanded access?

To answer these questions, medical specialists were interviewed in the Netherlands (n=14), Turkey (n=12) and the US (n=8). Regulatory pathways for expanded access differ between these countries but have conditions in common: the disease must be serious/life-threatening, an approved alternative therapy is not available, there must be potential for medical benefit, patients are not eligible for clinical trial participation, and there must be approval from the drug regulatory authority or inspectorate.

The interviews made clear that some doctors make use of expanded access programmes, but awareness of and attitudes towards expanded access differ in and between countries. These different attitudes are not the only hurdle to expanded access. In addition companies are not always willing to supply investigational drugs, there are reimbursement issues, and last but not least there are those who claim that expanded access undermines clinical research. So one could pose the question: do we *want* to increase access to unapproved investigational drugs? More information is needed to answer this question, and therefore as a follow-up study, a survey was recently sent to more than 5,000 medical specialists in the Netherlands to ask them about their experiences with expanded access in day-to-day practice. This survey will add to our understanding of the decision-making processes physicians use.

REGULATORY SCIENCE AFTERNOON SESSION:
THE CHALLENGES FOR RESEARCH IN SMALL POPULATIONS

The afternoon was introduced by **Dr Christine Gispen-de Wied (Medicines Evaluation Board /University Utrecht)** who reminded the audience that rare diseases inherently mean small numbers of patients, and therefore potentially new models and methods for Randomised Controlled Trials (RCT) should be developed to deal with these small numbers.[4]

Single Patient Outcome Measurement

One of the potential methods to be used is Goal Attainment Scaling (GAS), which is an individualized instrument with potential for outcome measurement in rare diseases. The first speaker, **Dr Hanneke van der Lee** from the AMC Amsterdam, presented details of this method.

One of the main challenges for drug evaluation is the often heterogeneous course of rare diseases. Traditional outcome measures, such as the Six Minute Walk Test, may not be applicable for all patients, whereas a measurement instrument such as GAS can evaluate the effect of an intervention on an individual basis, and may enable trials to include patients at different stages of their disease. It also enables patients to set individual goals together with their treating professional [Box 2].

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BOX 2: Goal Attainment Scaling: an individualized outcome

$$T = 50 + \frac{10 \sum w_i x_i}{\sqrt{(1-\rho) \sum w_i^2 + \rho (1-\sum w_i)^2}}$$

A systematic review published by Hanneke van der Lee and colleagues[5] showed that of the 38 articles on drug treatment, only 7 described measurement properties of GAS. This suggests that the validity, responsiveness, and reliability in drug studies are under-investigated. Moreover, validation was mainly in geriatric and rehabilitation studies, and usually in non-drug trials. Additionally, Hanneke van der Lee and colleagues performed a GAS simulation study to determine the optimal number of goals a patient can set, and the potential effect of weighting these goals. More goals did not necessarily improve the quality of the instrument; well-chosen goals were more important. The underlying disease should be well reflected by these goals, and goals should be highly associated with the expected outcome. This latter point increases the power of the measurement, which is important especially in studies for rare diseases. Overall, GAS seems a promising instrument for heterogeneous patient groups, but requires further validation in drug trials. As a first step, van der Lee and colleagues will apply GAS as an additional outcome measure in a phase III rare disease trial and assess its measurement properties. Finally, they will submit GAS to EMA for endorsement of its use as a Patient Reported Outcome in selected orphan drug trials, in line with the EMA requirement of 'clinical relevance' in their evaluation of orphan drugs.

N-of-1 trials in small populations

N-of-1 trials are 'single patient trials', which can be particularly useful in evaluating the efficacy of very rare diseases. **Dr Stephanie Weinreich**, who works at the VU University Medical Center, Amsterdam and also at the National Health Care Institute (ZiN) introduced the concept to the audience.

N-of-1 trials are characterized by episodes in which the patient gets both medicine and placebo but is unaware of the sequence in which they are given; so in effect it is a randomised placebo-controlled trial. In addition, neither patient nor doctor knows the sequence so the trial is also double-blind. To minimise interference between compounds, a wash-out period between treatments is used. After each episode the effect is measured [Box 3].

N-of-1 trials have limitations: they are only suitable for chronic, stable diseases and for symptomatic treatment. The treatment must have a fast onset and offset or there is a risk of carry-over from one episode to the next. But if the drug and the disease meet the methodological conditions, this method gives the highest form of evidence possible for individual patients. Moreover, statistical methods enable aggregation of multiple n-of-1 trials and so this could be an efficient method in rare diseases.

BOX 3: N-of-1 trials: clinicians' and regulators' perspectives

N-of-1 trials provide data about effectiveness at the patient level. When aggregated they provide information about groups, which licensing and reimbursement authorities need.
(Stephanie Weinreich 2016)

With this in mind, Stephanie Weinreich and colleagues set up a study to assess whether ephedrine could be used as an add-on treatment to acetyl cholinesterase inhibitors or low-dose prednisone in patients with Myasthenia Gravis (MG).[6] Based on power calculations, four patients were included in the study. The main question was: is there an effect in these four patients?

The effect of ephedrine in all four patients was positive and significant for both the primary (quantitative MG score) and secondary outcomes. After extrapolation to the population level the main outcome measure remained significant, but the secondary outcome measures did not. Responding to the results, ZiN concluded that the n-of-1 design was suitable for judgement on reimbursement for this indication, but that for clinical relevance further support is needed. The MEB acknowledged the statistical significance but was also of the opinion that clinical relevance needed further evidence. They also requested individual data and from these considered that "a clear, consistent treatment effect within a patient was not observed". This surprised the researchers as the extra information from n-of-1 trials (at an individual level) affected the evaluation at group level.

Stephanie Weinreich and colleagues plan to publish the regulator's responses taken from a scientific advice procedure provided by both organisations, which is unique in the regulatory environment. She concluded that from the regulatory perspective aggregated n-of-1 trials can provide evidence on effects at a population level, that for reimbursement you can use the n-of-1 trial, and that n-of-1 trials are rich in information which at the

same time may undermine confidence in group-level interpretations. Christine concluded that using this kind of information from regulators enhances transparency in the regulatory decision process.

Developments on statistical design and analysis of small population group trials

The last speaker of the day was **Prof Dr Kit Roes** from the University Medical Centre of Utrecht. Kit began his presentation with the EMA guidelines on research in small populations. These guidelines state that *"No methods exist that are relevant to small studies that are not also applicable to large studies. However … less conventional … methodological approaches may be acceptable if they help to improve the interpretability of the study results"*, and in the opinion of Kit these less conventional and new methodological approaches are needed for several good reasons: rare diseases are more often those for which there is still no treatment, and in these conditions we more often see great heterogeneity between patients. Then there are the challenges of choosing appropriate (clinical) endpoints and biomarkers, and of 'evidence synthesis' across trials because in the case of rare diseases we not only have too few patients but too few trials as well. As an example of the benefits of a less conventional new approach, Kit showed a classically designed RCT for an orphan drug in a rare disease (Fabry's disease) with a clinically irrelevant primary endpoint. It resulted in a negligible and non-significant effect of the experimental drug, while in fact there was a clear positive effect shown in the post hoc (non- conventional) analysis [Box 4].

Kit is one of the initiators of the Advances in Small Trials dEsign for Regulatory Innovation and eXcellence (Asterix) consortium[7]. Asterix is a novel, EU funded project focusing on developing more efficient and effective research designs for studying new drugs and treatments for rare diseases. The overall aim is to achieve more reliable and cost efficient clinical development of treatment for rare diseases and to stimulate the search for treatments for these devastating and largely ignored diseases. The main objectives are to develop design and analysis methods for single trials and series of trials in small populations, to include patient level information and perspectives in design and decision making throughout the clinical trial process, and to validate new methods and propose improvements for regulatory purposes. Unique to Asterix is the patients' direct involvement in the research process and their input in the design and analysis of studies.

A major component of the Asterix research programme is the development of a framework for guidance driven by disease and treatment characteristics, including clinical and statistical considerations based on some 100 EMA dossiers. With this framework it becomes possible to give tailored advice on the statistical and methodological options for trial design in rare diseases. For instance, as an alternative to power calculations based on the type I error rate, it may be preferable (and possible) to determine the optimal sample size for a clinical trial based on the disease population size. In addition, under the heading of 'Evidence Synthesis', data from previous studies can be used in new trials to reduce sample sizes and make clinical trials for orphan drugs more efficient. Existing data can also be used in a so-called 'Prospective meta-analysis'. Finally Kit mentioned the impact of these statistical and methodological ideas on Regulatory Science. In his opinion guideline development is okay but not enough. The EU needs more expert involvement in choosing and assessing the most appropriate study designs, especially in clinical studies with small groups.

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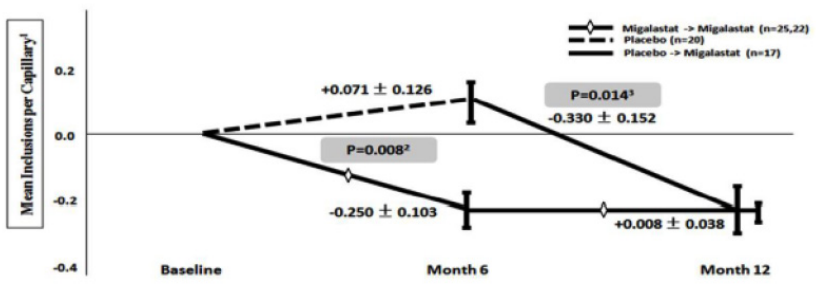
BOX 4: Non-conventional post-hoc analysis showing an effect, while the conventional approach did not.

Figure 4: AT1001-011: Change from Baseline in the Mean Number of GL-3 Inclusions per Kidney Interstitial Capillary



Post-hoc analysis In 50/67 patients with amenable mutations.

Plenary Discussion

Finally, Just Weemers invited all speakers to take part in a plenary discussion. The panel was completed by **Dr Michael Binks** (MD), Vice President Rare Disease Clinical Research at Pfizer and **Cindy Wang**, chair of the Patient Society Osteogenesis Imperfecta.

Referring to Hanneke van der Lee's presentation on GAS, Christine Gispen-de Wied asked Cindy Wang as a patient representative for her opinion on this. She answered that in her opinion research should focus on gaining more insight into the disease itself and that research for individual goals/outcome can be complementary to that. Michael Binks confirmed this view, but stressed that GAS does not solve the key problems in rare disease settings, but from the patient's perspective there is certainly quality of life value in such assessment because something very relevant to the patient is being measured. Bert Leufkens added from the regulatory perspective that when validating trial results for licensing, there is often a grey area with no sharp distinction between Yes or No. And here Quality of Life and Patient Reported Outcome measurements can be very helpful. "So this is not a game changer, but GAS data can tilt the decision to license a drug."

Christine Gispen-de Wied next addressed heterogeneity: What are the effects of a rigid application of exclusion criteria in clinical trials in small populations? "Aren't we far too strict?" To Michael Binks it is obvious that industry must make a scientific case for a compound's efficacy. And so they will do anything to improve the signal-to-noise ratio in the experiment. Kit Roes confirmed the importance of an optimal signal-to-noise ratio, which is difficult to reconcile with a broad inclusion. He therefore called for the development of different forms of clinical trial design to ensure answers to these big questions.

Eline Bunnik raised the point that we would not want a big discrepancy between what the drug does in the idealised situation during development and afterwards when it has been approved and is usually applied to a much broader and diverse patient population.

With regard to the confirmatory trial, Bert Leufkens pointed out that this cannot be avoided yet in the course of legislation for new drugs. At the same time it is important to proceed with the discussion on this and the search for alternative models.

"Can we come out of our comfort zone?" was the final question. **Dr Andre Broekmans** of Esher/Lygature believes we should take more risks to get real world evidence. He suggested bringing all stakeholders together to discuss what needs to be done to reduce uncertainties around getting the right evidence post-approval, starting with pre-approval, based on a limited dataset, acknowledging the problems and discussing how to add real value during practise. Just Weemers concluded that you cannot do this research without having all stakeholders present; not only industry, academia and regulators but patients also. This is the aim of the RSNN. Since its foundation a year ago, the network has expanded. We have been in contact with a lot of different people in academia, industry, and regulation, which has resulted in the first symposium in July this year where we focused on the use and regulatory aspects of biomarkers. Recently we published a summary report of the symposium in our first Newsletter and the RSNN has also got a spot on the FIGON website. So keep following the Network!

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