European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

European Reference Networks

8.3 ERN-EuroBloodNet report on actions to improve access to drugs for very rare hematological diseases and/or with clear impact on the clinical course of the disease

EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW PREVALENCE AND COMPLEX DISEASES

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DOCUMENT INFORMATION

8.3 ERN-EuroBloodNet report on actions to improve access to drugs for very rare hematological diseases and/or with clear impact on the clinical course of the disease

Report document

ERN: **ERN-EuroBloodNet (European Reference Network on Rare Hematological Diseases)**

Call: **HP-ERN-SGA-2018**

Type of action: **HP-SGA-PJ**

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Short Description

Report on the activities promoted by ERN-EuroBloodNet members to improve access to drugs for very rare hematological diseases and/or with clear impact on the clinical course of the disease.

Publication Date

30/06/2020

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1. INTRODUCTION

RARE AND ULTRA-RARE DISEASES OVERVIEW

Rare and ultra-rare diseases, often referred to as orphan and ultra-orphan diseases, affect very small numbers of patients. A rare disease (RD) is defined according to the European legislation as a condition presenting a prevalence threshold of not more than five affected persons per 10,000 individuals (Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products). The number of different RD in Europe is estimated between 6,000 and 8,000.

In contrast, a disease is generally considered to be ultra-rare if it affects one patient per 50,000 people (or, fewer than 20 patients per million of population) and most ultra-rare diseases affect far fewer than this as few as one per million or less. This poses a problem for the development of therapies because of the small number of subjects that can be recruited in clinical trials (CT). The number of these diseases is itself difficult to specify, in the absence of an exhaustive census or because they cannot be diagnosed. However, based on prevalence distribution tables such as those produced by Orphanet (Prevalence and incidence of rare diseases: Bibliographic data, Orphanet January 2020), it can be seen that this apparently very low threshold will nevertheless place the vast majority (probably more than 80%) of diseases classified as rare by regulation in the category of ultra-rare diseases. Ultra-rare diseases thus probably have more than 5,000 different entities.

Arguably, in the past few years interest in RD has grown, as demonstrated by the agendas of politicians and health authorities, but too little attention is still paid to ultra-rare diseases. European legislation was introduced in 2000 to stimulate the development of drugs for rare diseases so-called orphan drugs, much later than the US Orphan Drug Act of 1983. This legislation requires the pharmaceutical industry to have a right to: 1) obtain protocol assistance at a reduced rate; 2) access the centralized authorization procedure; 3) benefit from reduced registration fees; and 4) enjoy 10 years of market exclusivity after registration. This has led to the authorization by the European Medicines Agency of 124 new orphan drugs in the EU between 2000 and 2015, of which about one third are for ultra-rare diseases.

CHALLENGES OF DIAGNOSIS, DRUG DEVELOPMENT AND TREATMENT OF ULTRA-RARE DISEASES

Because of their great rarity and diversity, ultra-rare disease often presents unique public health challenges:

- Typically, few researchers or companies explore the disease, given the very small number of patients affected. Access to patients is complicated, which is constraining for the constitution of cohorts and their study. This reduces the chances of defining both the natural history of the disease and biomarkers.
- Often, very few physicians are familiar with diagnosing and treating the illness, leading to missed, delayed or inaccurate diagnoses even when an approved, effective therapy is available.

Biopharmaceutical companies face unique challenges as they seek to develop new, innovative therapies for patients with ultra-rare diseases. While nearly all drug development entails high levels of risk and investment, this is especially true in ultra-rare diseases. These challenges include:

- The need to identify sufficient numbers of patients to participate in CT, which often results in a large number of trial sites in multiple countries since each may only enroll one or two patients or none at all. Another important issue is how research should be carried out for ultra-rare diseases, along with the issue of quality. With no global consensus on the standard of care, this often leads to difficulties in identifying homogenous populations of these RD. Furthermore, with the limited data available from an incomplete understanding of the disease's history, it is often difficult to identify meaningful outcomes for CT. Clinical evidence on ultra-rare drugs for chronic diseases is frequently based on observations among small numbers of patients in short-term studies utilising surrogate outcomes rather than long-term trials. Typically, in such studies, the primary end-points are surrogate; the relationship between the surrogate end-point and survival or mortality or other clinically relevant end-points is not always clear.
- Increased regulatory risks since there is usually no approved therapy for a given ultra-rare disease, and no well-established road map for regulatory approval.
- Increased cost and risk for manufacturing ultra-orphan drugs, since most are complex biologics that require living cells for production (versus chemical drugs whose production is typically simpler and less expensive). Indeed the costs of developing as yet unknown compounds to treat ultra-rare diseases would thus remain out of all proportion to the financial return that investors could expect from them, unless they demanded exorbitant prices that health economies would not be able to tolerate.
- The need to engage in significant physician education, patient support and post-marketing research once an ultra-orphan therapy is approved.

However, a strategy has existed for years in the world of pharmaceutical research that aims precisely at removing the bulk of these obstacles: "repositioning". This term refers to the exploration of the possibilities of extending to other indications a compound that is already perfectly characterized, and even most often marketed, to other indications.

Consequently, finding a treatment for these diseases is a major public health challenge. In addition, national governments must develop strategies to drive clinical research, and incentives to encourage teaching hospitals to care for and investigate rare and ultra-rare diseases.

ERN-EuroBloodNet strategy to promote clinical studies in ultra-rare hematologic diseases

Following the desk research performed by ERN-EuroBloodNet in 2019 (Deliverable 7.1 Report on state of the art of Clinical Trials in Rare Hematological Diseases, SGA 811641), on rare haematological diseases, only 26 Rare hereditary anaemias (RHA) from the 105 disorders classified as RHA (25%) are currently covered by at least one CT. This means that for 3 out of 4 very rare RHA no CT is available, thus no new therapeutic option. RHA not covered by any CTs include in particular a) chronic hemolytic anemias due to membrane disorders or channelopathies, as Hereditary Spherocytosis, Hereditary Ellyptocytosis, and Overhydrated / Dehydrated hereditary stomatocytosis, b) constitutional dyserythropoietic anemias and most c) hemolytic anemias due to a enzymatic deficiency, d) constitutional sideroblastic anemias and e) constitutional anemia due to iron metabolism disorder. In addition, only 19% of the CT are open in Europe and from this, only around the 50% are active in ERN-EuroBloodNet members from only 5 member states.

It is urgent to improve the access to CT of patients affected by ultra-rare RHA across EU. ERN-EuroBloodNet has therefore started planning actions in this field.

2. OBJECTIVES

Despite the very small number of patients they affect, the impact that ultra-rare diseases have on patients, their families, and society is profound, as many are severe, chronic and progressive, with high mortality rates. Patients with severe and life-threatening ultra-rare diseases often live without hope as they have no effective treatment options and may face premature death. These ultra-rare diseases often present unique public health challenges.

In order to promote the to promote clinical research on ultra- rare hematologic diseases ERN-EuroBloodNet has established EuroBloodNet association, which aims to advance the care and treatment of very rare hematological diseases by conducting credible clinical trials whose results are intended to directly improve the prognosis and well-being of patients.

This deliverable details the EuroBloodNet Association principles, methods and means, as well as the first Clinical trial promoted by the entity in the context of Myelodisplastic Sysndromes.

3. TASKS

TASK 1. ESTABLISHMENT OF EUROBLOODNET ASSOCIATION

EUROBLOODNET ASSOCIATION has been announced on the Official Journal of the French Republic, associations and company foundations, in the Announcement n° 1327 75 – Paris ASSOCIATIONS Creations. Considering the French law of July 1st, 1901 relating to the contract of association; considering the French decree of August 16th, 1901 on public administration regulations for the implementation of the above-mentioned law; The French Prefect of Police, with a decision taken the January 19th, 2018, gives receipt to the President a statement dated: February 01, 2018 making known the constitution of an association with the title: EUROBLOODNET ASSOCIATION whose head office is located at the service d'hématologie séniors,– Trèfle 4 (head, Prof Pierre FENAUX) at hôpital Saint Louis – 1 Avenue Claude Vellefaux – 75010 PARIS. The receipt of CREATION Statement of the association is the n° W751243310.

The association is ruled by a board of directors, which includes members of EuroBloodNet scientific committee composed of:

- The President :Prof. Fenaux, oncological hub chair
- The vice-president :Prof. Béatrice Gulbis, non-oncological hub chair
- The treasurer: Prof. Régis Peffault de Latour

EuroBloodNet association aims to support ERN-EuroBloodNet actions, the European Reference Network for rare diseases in hematology.

TASK 2. EUROBLOODNET STRATEGY TO DEFINE MAIN SPONSOR AND DELEGATE SPONSOR AMONG ITS MEMBERS

Trials to optimise the management or new indications of old molecules will become increasingly important in the years to come. They require the inclusion of a large number of patients combined with the know-how of experienced investigators. These trials will therefore necessarily be European, and most of the time with academic promotion. This is even more evident in RD where testing a drug for its specific indication is only conceivable at European level. This approach requires networks of investigators, investigative structures, and the link to European structures.

EuroBloodNet association aims to promote clinical research on ultra- rare hematologic diseases in the optic of advancing the care and treatment of these diseases by conducting credible clinical trials whose results will directly improve the prognosis and well-being of patients.

In this frame, EuroBloodNet association fosters collaborative research activity especially In European, because the network activity gives an interactive research dimension. Structured clinical research networks promote the emergence and, above all, the implementation of new projects under optimal conditions of quality and efficiency. For this purpose, it has recruited a clinical research team from among its members responsible for promoting the trials and monitoring the data, thus allowing each member to develop his or her research project with the support of the association.

The main sponsor for each trial will be the university hospital of the principal investigator. Participation of other EU countries will be possible by defining delegate sponsors in those countries (generally university hospitals), according to the EU directive on clinical trials. Main sponsor will also cooperate closely with companies for drug storing and shipping, and for pharmacovigilance.

4. RESULTS

MDS-NEXT: First clinical trial promoted by EuroBloodNet Association

Myelodysplastic syndromes (MDS), represent clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis resulting in blood cytopenias, especially anemia. MDS with ring sideroblasts (MDS-RS) belong to "low risk MDS" (ie low risk of progression to acute myeloid leukemia), and are characterized by the presence of numerous ringed sideroblasts in the bone marrow, and presence of SF3B1 somatic mutation in marrow cells. MDS-RS are associated with profound anemia that tends, immediately or after some time, to become resistant to erythropoietin (EPO) and newer drugs, including Lenalidomide and the new agent Luspatercept. Thus, most MDS-RS patients become at some point red blood cell (RBC) transfusion dependent, with transfusions generally required at regular intervals. These frequent transfusions can induce transfusion-associated circulatory overload and, in the long term, iron overload accumulating in the liver, heart and endocrine glands.

RBC degradation during storage can contribute to several complications. In vivo and ex vivo studies demonstrate the increase storage duration may impair red blood cell oxygen delivery and affect immune, endothelial and hemostatic. The storage lesions can be explained by chemical oxidation, a central action that initiates oxidative stress. Several approaches have been proposed to reduce this oxidative damage.

Hemanext company found that red cell degradation is O2 dose dependent, and that if the O2 concentration is below 20% at the time of storage, it is possible to minimize degradation and optimize red cell quality. Hemanext has developed an oxygen removal and storage system for RBCcalled the Hemanext RBC Processing System to optimize this quality. This technology is intended to improve outcome for those patients dependent on RBC transfusions to survive.

In order to demonstrate both safety and performance objectives for Hemanext's RBC storage system and Hemanext's hypoxic RBCs, we will first perform in MDS-RS with RBC transfusion dependence a phase I study assessing full security of the Hemanext RBC concentrates. This will be followed by a prospective, multicenter, longitudinal, randomized, open label phase II study in RBC transfusion dependent MDS-RS comparing Hemanext RBC units with hypoxic storage and "classical" RBC concentrates, using RBC transfusion requirement as primary endpoint of the study.

EuroBloodNet association will act as trial sponsor, initially in French centers. Based on EU directives on clinical trials, the subsequently extension to other EU countries is expected. .

Other potential clinical trial to be promoted by EuroBloodNet Association

ERN-EuroBloodNet has already identified the conduction of the following academic CT in very RD in which pharmaceutical companies have not planned CT:

- Luspatercept (an inhibitor of the transforming growth factor beta (TGF-β) superfamily) in Congenital Dyserythropoietic Anemia type II (CDAII) and congenital sideroblastic anemias, diseases requiring require regular red blood cell transfusions. Luspatercept, in those disorders, should be able to induce differentiation of erythroid cells, improve ineffective erythropoiesis, correct anemia and limit iron overload.
- Senicapoc in dehydrated hereditary stomatocytosis (DHS), also known as hereditary xerocytosis, a ultra-rare hemolytic anemia characterized by a decreased red cell osmotic fragility due to a defect in cation permeability, resulting in red cell dehydration and compensated hemolysis of different degrees. No treatment is available for this condition. Senicapoc (also known as ICA-17043) is a potent blocker of the Gardos channel, a calcium-activated potassium channel of intermediate conductance, in the red blood cell. Preclinical studies and studies in transgenic models of SCD show that inhibition of potassium efflux through the Gardos channel is associated with an increased hemoglobin level, decreased dense cells and decreased hemolysis.

In addition, actions are also being conducted for the identification of CT using highly innovative treatments whose availability is limited in some EU-MS due to budget restrictions, lack of diagnostic procedures or various infrastructures. In this context, ERN-EuroBloodNet aims to contribute to set up conditions for implementation of such CT in those EU members and or specific centres.

5. CONCLUSIONS AND NEXT STEPS

A number of unique clinical, regulatory and commercial challenges are associated with the development of therapies for the treatment of RD, particularly ultra-rare diseases. Indeed, many therapeutic needs are still not covered by authorised drug therapies for the treatment of rare and ultra-rare diseases. Being a small market for the pharmaceutical industry, a significant part of therapeutic innovation in rare and ultra-rare diseases comes from academic research. According to "Where do new medicines originate from in the EU?" (Nature Reviews Drug Discovery 13, 92–93 (2014)), 17% of all drugs coming to the market come from academic research, including 11% for orphan drugs.

In this context, EuroBloodNet association aims to conduct clinical trials as part of its clinical research activity. This activity, which will cover ultra-rare haematological diseases for the benefit of patients, will be essentially academic and promote European partnerships.

EuroBloodNet is going to submit its first clinical trial in ultra- rare hematologic diseases for which it will be the sponsor. This trial concerning a medical device, will test innovative transfusion bags that could improve the living conditions of transfusion-dependent patients suffering from Myelodysplastic syndrome with ring sideroblasts (MDS-RS).

The promotion of MDS-NEXT through EuroBloodNet Association will represent the pilot exercise that will facilitate the consecution of two additional trials that are currently are in preparation, enriching the networking for collaborative projects at both, national and European level.

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https://ec.europa.eu/health/ern_en

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