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Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy

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Guideline on medicinal products for the treatment of Duchenne and Becker muscular dystrophy

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Executive summary

Recent advances in basic and clinical research have opened new perspectives for future therapeutic options in Duchenne and Becker muscular dystrophy (DBMD). The increasing number of clinical trials that recruit a rather small number of patients for these progressive disorders has raised several issues, including the study design, the choice of appropriate efficacy endpoints in general and the definition of reliable surrogate outcome measures [1, 2] as well as the need of subgroup analyses with respect to the heterogeneous patient population and the duration of the trials (e.g. long-term treatment goals [3]). As most of the cases of Duchenne muscular dystrophy (DMD) have an onset in early childhood, while the onset of Becker muscular dystrophy (BMD) covers a broader age spectrum, specific difficulties have been identified that pertain to diagnostic criteria, age- and stage related clinical relevance [4] and different safety aspects.

This Guideline is intended to provide guidance for the evaluation of medicinal products in the treatment of DMD and BMD; it is acknowledged that for several aspects the present document cannot give definite guidance due to the heterogeneity in phenotypes of both diseases and the expected treatment goals that also may vary according to disease status.

The present document should be conceived as general guidance and should be read in conjunction with other relevant EMA and ICH guidelines (see section 3).

1. Introduction (background)

Duchenne and Becker muscular dystrophies are rare diseases, DMD is life-threatening and shortens patient`s life substantially. DMD and BMD are recessive X-linked forms of muscular dystrophy. With respect to DMD patients, one out of 3500 – 6000 boys is born with this disease [6]. The figures for incidence in girls are highly variable among publications, related to the milder and highly variable clinical presentation. Regarding BMD about 1 in 20,000 boys is affected [7].

Duchenne muscular dystrophy is characterised by progressive symmetrical muscular weakness that affects proximal muscles more than distal muscles, often accompanied by calf muscle pseudo-hypertrophy. In most of the times symptoms are present before five years of age. Wheelchair dependency occurs before the age of 13 years. In about one third of the DMD patients there is cognitive decline and behavioural abnormalities. After 18 years all patients are affected by cardiomyopathy. Only few survive beyond the third decade; most patients die because of respiratory complications and heart failure due to cardiomyopathy [8].

Becker muscular dystrophy is characterised by a later onset and a generally milder clinical course. A remarkable variability of clinical expression exists [7]. Thus, weakness of the quadriceps femoris muscle could be the only symptom. Patients remain ambulatory for a variable period of their life and not all end up as wheelchair dependants. Most patients develop at some point in time dilated cardiomyopathy that is the most common cause of death. Mean age of death is in the mid-40s [8], but life expectancy could also be higher.

In DMD patients the dystrophin protein is deficient and non-functional, while in BMD patients it is with an altered size but with some residual function. The dystrophin gene is mainly expressed in skeletal and heart muscle and in alternative forms in the brain. In the muscle cell dystrophin is part of a sarcoglycan protein complex connecting the cell membrane with the contractile proteins. The loss of dystrophin function causes muscle fragility with muscle fibre loss followed by inefficient regeneration and subsequent progressive replacement of muscular mass with fibrotic and fatty tissue. The progressive damage of the skeletal muscles results in decrease in muscle strength, starting from lower extremities and gradually affecting all muscles.

The underlying molecular pathogenesis of DMD consists of a variety of mutations in the dystrophin gene. These could be classified into three main categories: gene deletions (mostly in the "hot-spot" central part of the gene; exons 45-53; 60-80%), duplications (7-11%) and small mutations (10-30%) including nonsense mutations, splice-site mutations and small insertions/deletions that disrupt the reading frame [9].

Genetic testing has become more broadly accessible over the last few years and is now a common part of the diagnostic process of DMD/BMD in treatment centres in the EU. Other diagnostic methods include serum creatine kinase, muscle biopsy data and emerging imaging modalities. With respect to muscle biopsy in DMD, there are the typical dystrophic transformations with absence of dystrophin, while there is a variable decrease of dystrophin in BMD [7]. Due to the considerably invasive nature of muscle biopsies, diagnosis of DMD and BMD is increasingly based on genetic testing rather than on qualitative assessment of muscle biopsy dystrophin.

At present, therapy is limited to symptomatic treatment. It encompasses medical and physical therapies to improve cardiac and respiratory function as well as corticosteroids to improve skeletal muscle strength and function. However, corticosteroids are not approved for treatment in this disease and their use is often limited due to significant side effects. Moreover, no consensus exists regarding the best treatment scheme [10]. In recent years, standards of care for DMD that normally are carried out by multi-disciplinary teams have been developed and were published in 2010 [6, 11]. Additionally therapies exist for orthopaedic corrections. With these interventions, patients are able to remain ambulant for a longer period of time and have a better life expectancy than in previous decades before.

Currently no curative treatments for DBMD exist. However, recent advances in basic and clinical research have opened new perspectives for future therapeutic options in DBMD [12] and various potential therapeutic approaches are under development: Gene therapy consists of introducing a transgene coding for full-length or a truncated version of dystrophin complementary DNA (cDNA) in muscles, whereas pharmaceutical therapy includes the use of chemical/biochemical substances to restore dystrophin expression (e.g. the stop codon read-through approach or exon skipping approach) or alleviate the DMD phenotype [9].

2. Scope

The scope of the guideline is limited to the X-linked recessive dystrophinopathy Duchenne (DMD), the most common and severe form of muscular dystrophy, and its milder version - Becker (BMD) muscular dystrophy. Other neuromuscular diseases are presently not within the scope of this guideline.

The presented guideline provides guidance for the conduct of clinical studies during the development of medicinal products intended for the treatment of DMD and BMD. This specifically pertains to the identification of the target population (e.g. ambulant vs. non-ambulant children and adolescents) and the choice of efficacy endpoints and safety parameters. Because of the disease´s chronic progressive nature that is accompanied by several comorbidities and its poor prognosis with shortened life expectancy, special attention should be paid to the study duration, the maintenance of effect and the long-term safety. The small number of patients available for studies and the high degree of variability could compromise the sensitivity of efficacy studies. These challenges will be considered in the document.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83 as amended and relevant CHMP and ICH guidelines, among them:

- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95 (ICH E6))
- Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95 (ICH E8))
- Dose-Response Information to Support Drug Registration (CPMP/ICH/378/95 (ICH E4))
- Pharmacokinetic studies in man – EudraLex vol. 3C C3A
- Statistical Principles for Clinical Trials (CPMP/ICH/363/96 (ICH E9))
- Choice of Control Group in Clinical Trials (CPMP/ICH/364/96 (ICH E10))
- Points to consider on adjustment for baseline covariates (CPMP/EWP/2863/99)
- Guideline on Missing Data in Confirmatory Clinical Trials (CPMP/EWP/1776/99)
- Points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99)
- Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95 (ICH E1A))
- Note for Guidance on the Investigation of Drug Interactions - CPMP/EWP/560/95
- Points to consider on application with 1. Meta-analysis; 2. one pivotal study (CPMP/EWP/2330/99)
- Note for Guidance on Clinical Trials in Small Populations (CHMP/EWP/83561/2005)
- Note for Guidance on Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99 (ICH E11))
- Ethical considerations for clinical trials on medicinal products conducted with the paediatric population, Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use (Final 2008)
- Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005)
- Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007)
- Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008)

4. Specific considerations when developing products for the treatment of Duchenne and Becker muscular dystrophy

Treatment of DMD and BMD may have different goals of treatment:

Improvement of symptoms and improvement of disability in affected patients:

At the present time treatment is mainly symptom-oriented including maintenance of muscle strength and function, prevention of respiratory and cardiac complications, orthopaedic corrections and physiotherapeutic interventions.

Certainly, symptomatic treatment may to some extent be related to improvement in disability, however it is not directly related to a delay in disease progression or disease modification. Therefore for regulatory purposes claims on symptomatic treatment and disease modification may require different types of evidence (see section 7.6.).

Modification of the natural course of the disease or increasing of survival:

The concept of disease modification in DMD/BMD is characterised by slowing down or stopping the accumulation and progression of disability. This includes the delay of disease onset and spread of disease to previously unaffected muscle groups as well as the delay in time to milestone events (e.g. time to wheelchair, assisted ventilation). Clinically, a sustained effect on disability progression has to be shown.

According to the mechanism of action of a potential medicinal product and the expected treatment goals the clinical development programme may vary with respect to the included patient population, endpoints and trial duration (please refer to section 7).

5. Patients characteristics and selection of patients

5.1. Diagnosis

Definitive diagnosis should be based on the clinical phenotype of DMD/BMD with characteristic clinical signs and symptoms (e.g. proximal muscle weakness, wadding gait and Gowers´ manoeuvre and progressive difficulty in walking), supported by serum CK levels and genetic testing confirming a mutation in the dystrophin gene. Exclusion of other neuromuscular disorders may involve electromyography and emerging imaging modalities (e.g. magnetic resonance spectroscopy); the latter being still in early stage of application.

In the majority of the cases the genetic defect can be detected which makes the diagnosis definite. A muscle biopsy could provide complementary information related to the functional expression of dystrophin. For patients without a confirmed genetic diagnosis, a combination of clinical symptoms, family history, elevated serum CK concentration, MRI and muscle biopsy is considered sufficient for a clinical diagnosis [7, 8], but it is not sufficient for inclusion in clinical trials in which potential medicinal products targeting certain type of genetic defects are investigated.

5.2. Inclusion criteria

Patients to be included in the clinical studies should have a confirmed diagnosis through genetic testing according to state of the art methods. This is particularly necessary for inclusion in mutation-specific therapy studies. Genetic testing will also ensure that subjects with some other forms of muscular disease are not included into the studies which may compromise the homogeneity of the study population (in terms of diagnosis) and may also lead to possibly unnecessary exposure to a drug which is not appropriate for other conditions.

The substantial disease heterogeneity between patients with Duchenne and Becker muscular dystrophy (e.g. the underlying mutation, the dystrophin level and (residual) functionality, different age of onset,

differences in severity and consequently different treatment goals) should be reflected in the product development programme. Due to differences in leading symptoms and consequently expected different treatment outcomes, both resulting from the stage of the disease, DMD and BMD patients should be studied separately.

Depending on the objective of the study, different subgroups of patients with respect to the stage of the disease (ambulant and non-ambulant) as well as to the developmental stage (e.g. child of pre-school age vs. schoolchild) should be selected a priori. In general, the patient population should cover a broad range, normally studies should start in older children with a step-down approach, unless the potential concerns with regard to safety or dosing can be addressed by extrapolation from similar products.

If the main treatment target is improvement in motor function, development of a medicinal product is recommended to start in ambulant males, who are able to walk a defined distance. In the second step one should focus on non-ambulatory patients. Alternatively, stratification according to the stage of disease (ambulant vs. non-ambulant patients) is considered necessary. In this case the outcome measures should be adapted according to the disease stage under evaluation. If the treatment is aimed at improvement of cardiac function, then subjects with dilated cardiomyopathy should be included and stratified if necessary according to the degree of cardiac insufficiency.

Regarding the progressive disease character, different cut-off scores for an appropriate scale should be used to include patients with a certain degree of severity to assure sensitivity to change. Thresholds for clinical severity of motor function impairment, respiratory and cardiac symptoms, associated cognitive deficits as well as further relevant co-morbid symptoms should be defined. However, at present only few assessment tools are adequately validated. (See also section 6).

5.3. Exclusion criteria

Excluded should be patients with:

- initiation of systemic corticosteroid therapy within 6 months or changes in dosing within 3 months prior screening
- any change in relevant concomitant therapies within 3 months prior to start of study treatment
- other neurological diseases or relevant somatic disorders that are not related to DMD/BMD, especially pre-existing pulmonary and cardiac disorders not attributed to DMD/BMD (consideration should be given to the use of a minimum standard of respiratory function as an inclusion criteria (e.g. FVC) to reduce the drop-out rate throughout the trial)
- subjects without a confirmed mutation in the dystrophin gene; subjects with another neuromuscular disease
- patients on other concurrent investigational medications

6. Methods to assess efficacy

6.1. Efficacy variables

The objectives of the study should be well defined according to the expected stage- and age-related improvement in certain symptom domains, e.g. walking, daily functioning, maintaining ambulant stage, use of upper limb in non-ambulant subjects, time to assisted ventilation or survival.

Functional mobility is considered as the most relevant outcome measure for patients affected by DMD and BMD. Treatment effects on functionality should be backed up by effects in the activities of daily living (ADL).

The primary pathophysiological effect of DBMD is a decline in muscle strength and motor function and these are therefore important parameters to measure. Muscle strength and motor function are closely related but quite distinct motor system parameters. Many additional factors other than muscle strength may influence the ability to walk [13]. Therefore, to provide evidence for a clinically relevant effect, a demonstrated effect on muscle strength always needs to be translated into parameters of motor function, or vice versa.

Two co-primary endpoints should therefore be pre-specified from the domains motor functioning and muscle strength. Depending on the treatment goals, measures of cardiac or respiratory function, e.g. in DMD-associated dilated cardiomyopathy, could also be selected as relevant primary endpoints.

Secondary outcome measures should include change from baseline in activities of daily living (ADL), respiratory and cardiac function, cognitive ability, health-related quality of life and caregivers survey. Although physical dependence, especially in DMD, is ultimately to be expected, maintenance of ADL (e.g. communication, eating, dressing, going to the toilet) is considered an important treatment goal [14]. Another potentially relevant outcome could be the reduction of corticosteroid use. However, due to the variability in clinical practices and the heterogeneity of the patient population in this respect, this may be considered as an exploratory endpoint.

Results for the co-primary outcome measures and the most important secondary endpoints should be discussed both in terms of clinical relevance and statistical significance. Related to the relatively small number of patients in such studies reference is also made to the Guideline for small populations. In order to support an estimate of clinical relevance, results should also be expressed in terms of the proportion of responders. Definition of responders and/or disease progression should be based on clinical considerations and be specified prospectively in the clinical study protocol.

6.2. Methods of efficacy variables measurement

From a regulatory point of view, no specific recommendation for the choice of the measurement tools can be made. Information should be obtained from a reliable informant, e.g. parent or caretaker, but also from the affected subject. Although self-reporting in children may not always be reliable, the development of measurement tools in this respect is strongly encouraged. Measurement tools should establish different limits according to subject age and/ or stage–related phenotype of the disease. Co-morbid symptoms should be rated with proper scales.

There are several measurement tools that are used in assessing motor functioning and disability. These are reflected in muscle functional testing that encompass e.g. measurement for upper and lower limb activity or walking speed (rather representing motor function on a lower level of muscular performances), as well as effects on ADL that more clearly represents the status of a certain muscle dysfunction, thus disability. However, it is still not clear, how parameters such as quantitative muscle testing (QMT), forced vital capacity (FVC) or timed activities correlate with quality of life, time to death and other life-changing events (e.g. time to wheelchair).

Motor function:

Improvement in motor function could be achieved by correcting or counter-acting the underlying genetic defect to restore the expression of dystrophin, or by increasing muscle growth and regeneration, or by modulating inflammatory responses. Therapeutic approaches targeting increase of

the dystrophin protein that are currently under development are gene or dystrophin protein replacement, dystrophin-splice-modulation therapy, specific drug treatment (e.g. the stop-codon read-through approach) or stem cell therapy.

For both ambulant and non-ambulant patients, the Motor Function Measure Scale (MFM) is a validated global scale for children from 6 years of age for different neuromuscular disorders, including DMD [15]. It offers a continuous assessment, regardless of disease severity and ambulatory status [16]. A short form, the MFM-20 could be considered in children down to as young as two years of age if justified.

Alternatively, for ambulant boys with DMD the non-specific North Star Ambulatory Assessment (NSAA) [16] that also includes timed items and the Hammersmith motor ability scale (HMAS) [17] can be used.

Other functional assessment grades are the Vignos´ lower limb score, the Brooke upper limb score and the GSGC (gait, stairs, Gowers, chair) assessment.

Ambulance is a relevant milestone in DMD patients. Recently, the 6-minute walk test (6MWT), originally developed as an assessment of cardiac and respiratory insufficiency, has also been used in a modified version as an outcome measure in DMD trials [18]. It has been validated in paediatric populations above the age of 5 years; normative data are available. By measuring endurance and the ability of walk, the test measures walking parameters that are of importance in the ambulant stage of DMD [17]. There are however several caveats with using the 6MWT as an outcome measure, which mainly pertain to a learning effect, to inter- and intra-personal variability, and to the definition of a clinically relevant difference.

Timed-function tests to assess timed activities exist for climbing a short flight of steps, walking a short, predefined distance (usually 10 meters), rising from the floor, and sit to standing from a chair. Although these tests were frequently used in the past, concern aroused with respect to the degree of assessor error in timing (especially for very brief tests as sit-to-stand from a chair), as the observed value of any measures is equal to the true value plus the degree of random error in bias [13]. Due to huge variability and small changes, the clinical relevance of results is often questioned. However, supportive evidence could be provided from these tests.

The validated Egen Klassifikation (EK) scale focuses on motor function in non-ambulatory patients [19].

Most of these tools have their shortcomings regarding the use of sum scores, the lack of long-term data and the definition of the minimal clinical important difference [20]. Taken into account the heterogeneity in DMD and BMD, disease-specific scales and tools that cover a broader range of disease severity should be combined. It is also recommended to combine different assessment tools, e.g. a functional scale and a timed-function test, to sufficiently assess relevant changes in motor function (e.g. endurance) and to transfer results into clinical relevance.

Assessment of muscle strength:

Muscle strength should be evaluated by clinical assessment using a validated tool. Options include manual muscle testing (MMT) also used as composite scores and quantitative muscle testing (QMT) scores such as hand-held-dynamometry (HHD).

Both tools have their shortcomings. HHD is often classified as preferred measure as it provides quantitative parametric data, whereas MMT is a subjective measurement method that depends on the perception of the assessor. The clinical significance of HHD data may, however, be less obvious than that of MMT as the correlation of a value in Newtons or kilograms with a change in muscle grade, or a change in functional ability is not clear. In contrast, with MMT, a grade less than 3 means that the participant cannot gain full range of movement against gravity, thus giving useful clinically relevant information for the evaluator [13].

Activities of daily living (ADL):

In the past, deficits of ADL were studied with the Functional Independence Measure (FIM) [21]. For wheelchair-dependent patients, the Barthel Index aims at quantifying the degree of functional assault for activities of daily living. Generally, the chosen tool should assess the age- and stage- related activities that are of most importance for the included patient population (e.g. eating, bathing, clothing, climbing stairs).

Survival and time to treatment failure:

Survival time or alternatively time to tracheostomy or time to permanent continuous ventilation are relevant endpoints in advanced stages of disease. As their measurement requires long lasting trials unless patients in advanced stages of disease are included, such assessments might be done as a post approval commitment. Criteria for tracheostomy and continuous ventilator dependence should be pre-specified since these can vary among countries and regions.

Respiratory function:

All trials should include testings of respiratory function. Measurement of forced vital capacity (FVC), vital capacity (VC), peak expiratory flow (PEF), forced expiratory volume in one seconds (FEV1), maximal inspiratory pressure (PImax) and other variables by spirometry should be done according to current standards and methods. Assessment of FVC is in particular essential in non-ambulatory patients where pulmonary dysfunction becomes relevant. It is acknowledged that pulmonary function tests are difficult to perform in non-ambulant patients with poor reproducibility.

Cardiac monitoring:

Assessment of cardiac function and its change during the trial can be performed through various measurements, e.g. echocardiogram, heart rate, blood pressure, changes in left ventricular ejection fraction (LVEF).

Assessment of Quality of Life:

A disease specific module of the PedsQL (Pediatric quality of life inventory), the PedsQL 3.0 Neuromuscular Module (NMM) has recently become available that could be administered together with the PedsQL 4.0 Generic Core Scales [4] [22].

Assessment of cognitive impairment:

Cognitive deficits or behavioural problems are noted in many DMD patients. Therefore, improvement or lack of deterioration in cognitive function might be a relevant clinical achievement. Neuropsychological tests should be used to assess cognitive function and/or behavioural changes. However, experience of neuropsychological tests in DMD and BMD patients within clinical trials is limited; therefore their use is still considered exploratory.

Muscle composition and muscle damage:

Serum CK levels, muscle dystrophin expression and reduction in inflammatory infiltrates still have their limitations as surrogates. Based on the fact that the currently existing methodologies to quantify dystrophin from muscle biopsies are debatable regarding the robustness and the precise quantification of extremely low levels of dystrophin, quantification of dystrophin protein from repeat muscle biopsies currently could be considered only as an exploratory endpoint for clinical efficacy. In cases where the mechanism of action of the therapy is related to the restoration of dystrophin expression, detection of dystrophin in muscle tissue could provide supportive information as a pharmacodynamic marker for proof of concept.

At this stage, there is no suitable biomarker that could be a primary or key secondary endpoint in phase III studies, but their development is encouraged.

CK is not considered a useful parameter to follow disease progression given its inconsistency in the course of disease.

7. Strategy and design of clinical studies

7.1. Extrapolation

The question of extrapolation in fact concerns two different aspects:

The first is the extrapolation of efficacy to various degrees of disease severity in a population with the same (group) gene defect (e.g. that can be corrected by the same exon skipping strategy).

The second is the extrapolation of efficacy results between patient populations with different groups of mutations.

For instance currently there is lack of information whether the effect and the safety of a certain anti-sense oligonucleotide (AON) is comparable within different stages of the disease, which also refers to the extrapolation to younger or older patients. Although it might be assumed that exon skipping will induce dystrophin expression irrespective of disease stage, the effect of this dystrophin in subjects with different degrees of muscle tissue being replaced by fat and fibrous tissue can be expected to result in a different response in muscle strength and function

With respect to differences in the underlying gene defect, differences in disease onset, the progressive course of the disease and different phenotype in DMD and BMD it is impossible to extrapolate results from exploratory trials or risk-benefit evaluation from BMD (mainly adolescents/young adults) to DMD (mainly paediatric patients) or vice versa. Hence separate clinical programmes (including exploratory studies) for both patient populations are considered mandatory unless a reasonable justification on a joint approach could be provided.

Generally, the extrapolation of data from studies with products targeting a certain mutation in the dystrophin gene to products targeting another mutation is considered a challenge that also depends on the underlying mode of action of the product. The wide range of mutations in the dystrophin gene requests at least for separate pharmacodynamic studies in different types of mutations (e.g. for each oligonucleotide with respect to exon skipping). Moreover, there is a lack of experimental data that corroborates the assumption of comparable efficacy and safety of different AONs in the treatment of DMD. However, depending on the mode of action of the product, specific types of mutations could be examined together (e.g. read-through of different nonsense mutations).

7.2. Pharmacodynamics

The proposed mechanism of action of a new product should be described and discussed in relation to possible testing in available animal models which are currently limited. (E. g. the mdx mouse is considered a poor model of the DMD phenotype, while the predictive value of results in the golden retriever muscular dystrophy dog is still unknown). In addition, the changes in biological parameters seen in patients or healthy volunteers (if appropriate) should be addressed.

It should be explored, whether the pharmacodynamic effect is similar in different stages of the disease (e.g. restoration of dystrophin in early and advanced stages of the disease).

The dystrophin protein (with truncated but functional variants) is accepted as surrogate marker for proof of concept studies in products aiming at inducing dystrophin synthesis. Biopsies should be minimised, but performed when necessary. The obtaining, storing, transport of muscle biopsies, and the assessment of protein expression should be standardized and performed according to international standards.

7.3. Pharmacokinetics

The usual PK programme may be replaced by an adapted one according to the mode of action of the new compound e.g. applicability in healthy volunteers. If feasible, pharmacokinetic studies may start with adults for safety reasons, e.g. first experience. Based on PK/PD modelling and simulation, these first exposure data would in principle allow a reduction in the number of children needed.

Sparse sampling approach is recommended in younger children, with PK in a preferred optimized design. Based on adequate support by pre-clinical data and PK modelling and simulation, extrapolation of PK data across different age groups might be sufficient. However, if pharmacokinetic differences in children, adolescents as well as young adults are expected, investigation of the pharmacokinetic profile for each age cohort is needed.

7.4. Interactions

The note for guidance on drug interactions should be followed to investigate possible pharmacokinetic and pharmacodynamic interactions. Data on pharmacodynamic interactions with other treatments of the disease are important (in particular corticosteroids, cardiac and pulmonary medications).

If applicable, the Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007) and the Guideline on safety and efficacy follow-up-risk management of advanced therapy medicinal products (EMEA/149995/2008) should be followed as well.

7.5. Exploratory studies

Proof of concept and dose-finding for a new product should be established in a preferably homogeneous patient group without relevant co-morbidities.

7.6. Therapeutic confirmatory studies

Patient population

In confirmatory trials, the efficacy and safety of the product should be studied in the broad range of patients (e.g. with respect to comorbidities (e.g. pulmonary diseases) or various manifestations of the disease) that the investigational product is intended to treat.

Characteristics of patients to be included in the studies may vary according to the mechanism of action of the product and its expected effect. This can differ according to the underlying mutation, characteristics of abnormal dystrophin (if present e.g. in BMD), stage of disease and hence different treatment goals and measurement tools.

Separate studies are preferred according to the disease stage and/or the outcome parameters, or at least those groups should be studied in a single trial with pre-specified stratification of subgroups including sufficient number of patients to allow for comparison in the different disease stage groups. However, consistency over the subgroups would add to supportive evidence.

In studies for symptom or disability improvement, the patient population to be included should be characterised by clear symptoms that might improve. In contrast, the patient population for disease modifying therapies could also include phenotypic unobtrusive patients (with no or only few symptoms) which may be prone to deterioration.

7.6.1. Short-term studies

Study design

Confirmatory trials to show symptom or disability improvement should be randomised, double-blind, parallel-group and possibly placebo controlled.

The preferred design to show a disease modifying effect or survival increasing is a time to event design where the event is defined as worsening on a functional or symptom scale or time to milestone event.

Choice of control group

In general at present, for a product with a new mechanism of action, the test product should be compared to placebo. Nevertheless, this allows e.g. for corticosteroids as standard of care, since all subjects in all treatment arms will receive as background therapy standard of care (e.g. corticosteroids) and co-medication. The decision to include a placebo control will also be influenced by the number of affected patients and the availability of some data from other compounds with the same mechanism of action (please refer also to section 7.1).

The use of historical controls is not considered appropriate due to a huge variability in patient populations, standard of care and co-medication in various times and treatment centres.

Study duration

The duration of the studies should correspond to the mechanism of action of the investigational product and the intended treatment goal. Trials investigating symptomatic treatment should last 3 months, trials to show an improvement of disability at least 6 months.

Confirmatory studies with products intended to modify the course of the disease or to increase survival should be long enough to show a clear effect on disability progression.

Methodological considerations

The population to be studied will consist of a considerable heterogeneous study population with respect to the stage of the disease, co-morbid symptoms, concomitant supportive care and steroid treatment (corticosteroid treatment versus corticosteroid naive patients). The effect of the investigated product has to be clearly separated from effects received from concomitant medication (e.g. steroids, pulmonary or cardio protective agents).

Baseline care should be unified as much as possible to prevent results from being confounded by variable supportive care such as clinical care, physiotherapy, orthopaedic, respiratory, psychosocial management of DBMD and cardiovascular medications. If appropriate, stratification could be considered according to background therapy.

Sample size should be calculated based on the treatment effect that is clinically relevant. The number of required patients to be included in clinical studies will particularly vary according to the number of affected patients. For very rare mutations it is obvious that only few patients can be studied. For details on the statistical analysis refer to the statistical guideline (ICH 9) as well as the Guideline on Missing Data in Confirmatory Clinical Trials (CPMP/EWP/1776/99 Rev.1).

Care should be taken to ensure that follow-up of patients is as complete as possible for as many patients as possible, even after discontinuation of treatment.

Some specific recommendations

To illustrate the above mentioned considerations a few examples are given below although it is known that the list is not exhaustive:

Clinical studies to demonstrate efficacy for a symptom improving agent could include patients with different stages of disease and should last 3 months. Primary endpoints should be selected from domains corresponding to the symptoms of relevance.

In ambulant boys clinical studies to demonstrate efficacy of a disease modifying agent (e.g. enhancing some level of dystrophin) the study duration is dependent on the sensitivity for the event of the population included. Primary endpoints should be in terms of time to milestone events; activities of daily living should be selected as important secondary endpoint.

Also clinical studies to demonstrate efficacy in a disease modifying agent in non-ambulant patients (advanced stage of disease) depend in their duration on time to event. Primary endpoints would accordingly be measurements of upper limb function and muscle strength. Again, ADL should be selected as important secondary endpoint. In more advanced disease stages the primary endpoint should derive from the domain of cardiac and/or pulmonary capacity and survival.

7.6.2. Long-term studies

Because of the chronic and progressive course of DMD/BMD, long-term effects on safety and efficacy (e.g. neutralisation of effect) need to be investigated. This may vary depending upon the investigated agent profile. If considered necessary (e.g. for medical products intended for symptom improvement), data collection may be warranted in an extension study within the post-approval setting.

7.7. Studies in special populations

For DMD the paediatric population is considered to be the central target population as the disease has an onset during early childhood. BMD is characterised by a later onset. In this context adults (and rarely elderly) are considered a special population.

Special ethical considerations and safety concerns in children have to be followed. Alternative strategies for dose-finding may be necessary in the youngest age group.

If certain subgroups are not studied (e.g. extremes of clinical severity) extrapolation should be justified in the dossier.

Adults / elderly

The age of inclusion is in principle unlimited in adults, although elderly subjects are not expected to be available for clinical investigation.

8. Clinical safety evaluation

8.1. General recommendations

In general the content of ICH E1 should be taken into consideration.

Identified adverse events (AE) should be characterised in relation to age, the dose, the duration of the treatment and other relevant variables. Assessment of adverse events, especially those predicted by the pharmacodynamic properties of the investigational product should be performed using a systematic methodology. Clinical observations should be supplemented by appropriate laboratory tests and ECG recordings.

8.2. Specific adverse events

Specific adverse effects related to off target effects of (gene) therapy should be monitored according to signals from the preclinical and early studies.

A major category of products developed or tested in DBMD are considered to target the primary pathophysiological defect by restoring expression of dystrophin. When treatment with use of antisense oligonucleotides which alters the synthesis of a particular protein is applied, special attention to accumulation should be given, respectively renal and hepatic effects. With respect to gene replacement therapy, special attention should be given to the occurrence of immunological side effects (e.g. serious infections and autoimmune disease).

Clinical exacerbation or deterioration could be expected if treatment is stopped. Due to the relatively long half-life of the dystrophin protein acute effects would not be expected. This should be anticipated and followed in studies accordingly.

Central Nervous System (CNS) adverse reactions:

Behavioural changes should be assessed if effects on CNS are expected.

Cardiovascular adverse reactions:

Special attention should be paid to cardiotoxicity, e.g. arrhythmias and conduction disorders. The need for ECG tracing before starting on the investigational product should be addressed. Depending on the class of the investigated medicinal product it might be necessary to closely monitor cardiac safety in all patients. In patients with dilatative cardiomyopathy a deterioration in cardiac function could be due to lack of efficacy on cardiac function (of the test treatment), due to natural course of disease, or due to an adverse effect. The distinction of these might be problematic.

Endocrinological adverse reactions:

Special attention should be paid to weight gain and growth (retardation) in children. Distinction should be made between the effect of corticosteroid therapy and the test therapy.

Depending on the pharmacological properties of the new therapeutic agent, the investigation of neuroendocrinological parameters (e.g. delayed puberty) may be necessary over an adequate period of time.

8.3. Long-term safety

Since DMD is a chronic progressive disease with onset in early childhood, and lifelong treatment is anticipated, long-term safety of the therapeutic interventions has to be carefully established. Special attention should be drawn towards the effects on the developing brain and body (in particular the endocrine system and CNS). Careful consideration should also be given to AEs related to long-term exposure and accumulation of the test drug (in particular relevant for oligonucleotides) in parenchyma organs.

Long-term safety data can be generated in open extensions of short-term studies and/or by specific long-term trials. Studies should last for at least 12 months, and prospective follow-up for a longer period of time should be part of the Risk Management Plan (RMP) post-licensing. A registry is advised as part of the Risk Management Plan.

For substances that are already approved in another indication, extrapolation of parts of the safety data to the DBMD population could be considered.

Definitions

Exons: The portions of a gene which contain coding DNA sequences.

Introns: The parts of a gene containing non-coding DNA sequences. Adjacent exons are separated by introns, which are later removed from the RNA transcript via the splicing mechanism.

Splice-modulation: This procedure aims at correcting genetic defects by molecular manipulation of the pre-messenger RNA. This is mostly mediated by antisense oligonucleotides (AO) or other short complementary sequences. The aim is to modulate the pre-m RNA splicing which results in a different mRNA (with exclusion of one or more exons).

Exon skipping: A mechanism based on masking part of the pre-mRNA in such a way that the splicing machinery skips over one or more exons. As a result, mRNA lacking some exons is produced which codes for a shorter protein.

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List of Abbreviations

ADL: Activities of daily living

DMD: Duchenne muscular dystrophy

BMD: Becker muscular dystrophy

DBMD: Duchenne/Becker muscular dystrophy

CK: creatinine kinase

AEs: adverse events

FVC: Forced vital capacity