Stakeholder cooperation to overcome challenges in orphan medicine development: the example of Duchenne muscular dystrophy

Volker Straub, Pavel Balabanov, Kate Bushby, Monica Ensini, Nathalie Goemans, Annamaria De Luca, Alejandra Pereda, Robert Hemmings, Giles Campion, Edward Kaye, Virginia Arechavala-Gomeza, Aurelie Goyenvalle, Erik Niks, Olav Veldhuizen, Pat Furlong, Violeta Stoyanova-Beninska, Matthew J Wood, Alex Johnson, Eugenio Mercuri, Francesco Muntoni, Bruno Sepodes, Manuel Haas, Elizabeth Vroom, Annemieke Aartsma-Rus

John Walton Muscular Dystrophy Research Centre and MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK (V Straub MD, K Bushby MD, MEnsini PhD, O Veldhuizen, A Aartsma-Rus PhD)**; European Medicines Agency, Human Medicines Evaluation Division, Scientific and Regulatory Management Department, CNS and Ophthalmology Office, London, UK** (P Balabanov PhD, M Haas PharmD)**; Department of Child Neurology, University Hospitals Leuven, Leuven, Belgium** (N Goemans MD)**; Unit of Pharmacology, Department of Pharmacy—Drug Sciences, University of Bari, Bari, Italy** (A De Luca PhD)**; Duchenne Parent Project, Madrid, Spain** (A Pereda)**; Medicines and Healthcare Product Regulatory Agency, London, UK** (R Hemmings)**; BioMarin Pharmaceutical, Developmental Sciences, Novato, CA, USA** (G Campion MD)**; Sarepta Therapeutics, Cambridge, MA, USA** (E Kaye MD)**; Neuromuscular Disorders Group, BioCruces Health Research Institute, Barakaldo, Spain** (V Arechavala-Gomeza PhD)**; Université de Versailles Saint Quentin en Yvelines, Inserm U1179, Montigny le Bretonneux, France** (A Goyenvalle PhD)**; Leiden University Medical Center, Leiden, Netherlands** (E Niks MD, A Aartsma-Rus)**; Parent Project Muscular Dystrophy, Hackensack, NJ, USA** (P Furlong)**; Medicines Evaluation Board, Utrecht, Netherlands** (V Stoyanova-Beninska MD)**; Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK** (M J Wood PhD)**; Joining Jack, Wigan, UK** (A Johnson)**; Pediatric Neurology, Catholic University, Rome, Italy** (E Mercuri MD)**; Dubowitz Neuromuscular Centre and MRC Centre for Neuromuscular Diseases, University College London Institute of Child Health and Great Ormond Street Hospital, London, UK** (F Muntoni MD)**; Faculdade de Farmácia, Universidade de Lisboa, Lisbon, Portugal** (B Sepodes PhD)**; and United Parent Projects Muscular Dystrophy, Amsterdam, Netherlands** (E Vroom DMD)

Correspondence to:

Dr Annemieke Aartsma-Rus, Department of Human Genetics, Leiden University Medical Center, 2333 ZA Leiden, Netherlands **a.m.rus@lumc.nl**

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Duchenne muscular dystrophy is a rare, progressive, muscle-wasting disease leading to severe disability and premature death. Treatment is currently symptomatic, but several experimental therapies are in development. Implemented care standards, validated outcome measures correlating with clinical benefi t, and comprehensive information about the natural history of the disease are essential for regulatory approval of any treatment. However, for Duchenne muscular dystrophy and other rare diseases, these requirements are not always in place when potential therapies enter the clinical trial phase. A cooperative eff ort of stakeholders in Duchenne muscular dystrophy-including representatives from patients' groups, academia, industry, and regulatory agencies—is aimed at addressing this shortfall by identifying strategies to overcome challenges, developing the tools needed, and collecting relevant data. An open and constructive dialogue among European stakeholders has positively aff ected development of treatments for Duchenne muscular dystrophy; this approach could serve as a paradigm for development of treatments for rare diseases in general.

Introduction

Developing treatments for genetic diseases poses unique challenges, as shown by the example of Duchenne muscular dystrophy,

a rare, progressive, muscle-wasting disease affecting about one in 5000 newborn boys.[1,2] Duchenne muscular dystrophy is caused by mutations abolishing production of the muscle fibre-stabilising protein dystrophin. Many experimental therapeutic strategies are being pursued. However, when some of these treatments transitioned into the clinical trial phase, crucial elements for their assessment were absent, including comprehensive data for natural history, meaningful outcome measures assessing clinical benefit, correlation of outcome measures with natural history, and pharmacodynamic biomarkers. During a meeting in 2009 organised by TREAT-NMD and hosted by the European Medicines Agency (EMA),[3] major bottlenecks in development of treatments were identified. This meeting gave rise to a cooperative effort among stakeholders—patients and advocacy groups, academics, health-care professionals, and industry— aimed at collecting the missing data and developing the tools needed. At the same time, European Union (EU) regulators began working on guidelines to support the development of medicinal products for the treatment of Duchenne and Becker muscular dystrophies.[4]

In this Policy View, we will use the example of Duchenne muscular dystrophy to outline how the collaborative effort of stakeholders in Europe can stimulate and assist orphan medicine development in the EU, with a focus on developing functional outcome measures, biomarkers, and regulatory guidelines, and on collecting longitudinal data for natural history (panel 1). We will also discuss future aspects of treatment development for Duchenne muscular dystrophy.

Duchenne muscular dystrophy and therapeutic strategies

Duchenne muscular dystrophy is caused by mutations in the dystrophin-encoding *DMD* gene.[5] Without functional dystrophin, muscle fibres are susceptible to damage, resulting in chronic degeneration and replacement by connective and fat tissue, causing progressive muscle wasting and weakness.[5–7]

Up to now, one compound, ataluren, has received conditional marketing authorisation in the EU for the treatment of ambulant patients with Duchenne muscular dystrophy aged 5 years and older with a nonsense mutation (causative mutation in roughly 13% of patients).[6,8,9] Other treatments are in clinical development, many of which have obtained orphan medicine designation in the EU (appendix). Exon skipping—the most advanced approach—aims to correct the disrupted reading frame in dystrophin transcripts, enabling production of a partly functional protein, as found in patients with the less progressive Becker muscular dystrophy.[10] Exon skipping is induced by short, chemically modified, DNA analogues (anti- sense oligonucleotides). Because mutations cluster, skipping particular exons applies to fairly large groups of patients.[6,9] A marketing authorisation application has been filed with the EMA for antisense oligonucleotides targeting exon 51 (applicable to about 13% of patients).[6,9]

Care standards for Duchenne muscular dystrophy

Irreversible loss of the ability to walk, self-feed, sit independently, and breathe without assisted ventilation (figure). These events are life-changing for affected children and their parents, with patients relying on full-time help in the later stages of the disease. Cardiac problems progress inevitably, leading to severe cardiomyopathy and premature death.

Standards of care have been generated and dissemi- nated in a collaborative effort of patients' organisations and TREAT-NMD, which was coordinated and supported by the US Centers for Disease Control and Prevention (CDC).[11–13] Multidisciplinary care (panel 2) focusing on all aspects of the disease has resulted in a slower disease progression, extending patients' mean life span to the third and fourth decade, when death generally occurs because of respiratory or heart failure. Nevertheless, in several European countries, adults and children with Duchenne muscular dystrophy receive suboptimum care,[18,19] and care standards for adults need to be developed further.[20] Findings of large multicentre trials show that variability in care generates noise in outcome variables.[21–23]

Duchenne muscular dystrophy has evolved from a paediatric disease to a severe and chronic adult condition. With increasing age of patients, the management of swallowing and feeding difficulties, smooth muscle involvement in bladder and intestinal dysfunction, and issues of social integration and quality of life will need further attention. A coordinated multidisciplinary approach addressing all factors that will determine health and quality of life should be guaranteed in the transition to adult care.

The regulatory process in the EU

Risk–benefit assessment

EU legislation requires that marketing authorisation for a medicinal product is refused if the risk–benefit balance is not deemed favourable, if therapeutic efficacy is insufficiently substantiated, or if the qualitative and quantitative composition of the medicinal product is not controlled appropriately. Assessment of quantified and well understood risks and benefits of a potential treatment is, therefore, key in the process of medicine regulation. To enable regulators to conclude on risk–benefit ratio, reliable measurements to identify and quantify risks and benefits need to be provided. Subjective judgment, input from stakeholders, and previous decisions for other products in the same area of medicine also contribute to risk–benefit assessment. To make decisions as explicit and transparent as possible, regulators have adopted a systematic and structured approach to risk–benefit assessment. For products that receive marketing authorisation, the EMA provides relevant information on the risk–benefit assessment in the European Public Assessment Report (EPAR). Moreover, patients' participation in risk–benefit assessment is ensured through a framework allowing them to take an active part in regulatory workshops, scientific advisory groups, scientific advice meetings, and committee discussions.[24,25]

Regulatory methods

Regulatory methods are in place worldwide to facilitate the development of medicinal products. Disease-specific guidelines describe regulators' preferences and standards for the demonstration of quality, safety, and efficacy of medicines. For

Duchenne muscular dystrophy, a draft guideline was published by the EMA in March, 2013, discussed among stakeholders,[26] and has now been published.[4] Furthermore, the US Food and Drug Administration (FDA) has published draft guidelines.[27] Regulatory agencies also provide scientific advice at anystage of the development of a medicinal product to helpinvestigators conduct appropriate studies to support a future marketing authorisation. Moreover, the EU offersa range of incentives to specifically encourage the development of orphan medicines (panel 3).

For rare diseases such as Duchenne muscular dystrophy, increased uncertainty about risks and benefits is more likely to be identified at the time of the assessment. However, specific approval mechanisms exist in the EU to enable early access to medicines fulfilling an unmet medical need in a fatal disease such as Duchenne muscular dystrophy, subject to the provision of post-marketing data (eg, conditional approval).[30] Furthermore, the EU regulation on orphan medicinal products provides market exclusivity for 10 years for a product that has obtained a marketing authorisation.[28]

The EMA has developed a scheme for priority medicines (PRIME) to optimise the development and accelerated assessment of medicinal products of major public health interest, such as those for rare diseases. PRIME is based on enhanced interaction and early dialogue with medicine developers; the scheme was launched in March, 2016.[31]

Outcome measures

The primary pathophysiological effect of Duchenne muscular dystrophy is a decline in muscle strength and motor function; therefore, these are important outcomes to measure. Any potential outcome measure to be used in Duchenne muscular dystrophy should be able to reliably detect and quantify a clinically meaningful effecton patients.[26]

Functional outcome measures

Regulatory requirements in the EU postulate that anobserved treatment effect needs to lead to a clear clinicalbenefit. Therefore, functional improvement or a delay inprogression and deterioration are judged relevantoutcomes for patients with Duchenne muscular dystrophy.To assess gross motor function, the 6-min walk test(6MWT) and the North Star Ambulatory Assessment(NSAA) are used as primary endpoints in most trials inambulant boys with Duchenne muscular dystrophy.[32,33]

A subset of ambulant patients with behavioural andcognitive problems cannot comply with these assessments, but well defined inclusion and exclusioncriteria will help to enrol those individuals who arewilling and able to comply with all clinical trial protocolrequirements and procedures. When the first trials forDuchenne muscular dystrophy were initiated, detailedlongitudinal data for the 6MWT were scarce. Because ofcoordinated efforts of stakeholders, data are nowavailable describing the evolution in this outcome over12, 24, and 36 months in natural history studies done inItaly and Belgium and by the Cooperative InternationalNeuromuscular Research Group (CINRG).[9,34–37] Based onthese data, we can depict longitudinal performance:young boys show some improvement in their 6MWTand NSAA scores up to the age of 7 years, butdeterioration usually takes place after this age.[32,34,37] Similar results have been recorded with cutoff values atbaseline for the 6MWT (above or below 350 m).[32,34,37] The combination of age and baseline cutoff values for the 6MWT has enabled identification of distincttrajectories of progression in different subgroupssubdivided by age and baseline values, which can beuseful for interpretation of clinical trial results. However, the acceptability of historical controls in clinical trials is
still a matter of discussion with regulators.[26,38]

The rate of functional decline and its predictive value on subsequent loss of ambulation has been established for the NSAA from a large database (UK North Star network) and for the 6MWT using data from CINRG,and this work was useful for postulation of the expectedminimal clinically important difference (MCID).[32,34,37,39] Furthermore, knowing the rate of decline and expected variation enables stratification and power calculations. Any target effect size should be discussed in advance with regulators to define expectations and agree on what constitutes a clinically relevant change in a given experimental setting. Evaluation of quality of life is an important aspect of treatment assessment. In patients with Duchenne muscular dystrophy, a strong correlation was noted between the 6MWT and the global Pediatric Outcome Data Collection Instrument (PODCI)—a health-related quality-of-life measure of functional ability. Even at highlevels of disability, small increases in the 6MWT lead to meaningful changes in quality-of-life scores.[39]

New functional outcome measure scales

By definition, the 6MWT and NSAA cannot be used in non-ambulant individuals. Since the average age at loss of ambulation is roughly 10·5 years,[40] and median survival of patients is about 30 years,[41,42] most people with Duchenne muscular dystrophy are non-ambulant. Toaddress this issue, a collaborative international group—including boys with Duchenne muscular dystrophy and their families—developed the Performance of Upper Limb scale to assess upper limb function in ambulant and non-ambulant patients with the disease.[43–45] The scale has been validated for clinical use against other functional measures (eg, the 6MWT),[46] and longitudinal data are emerging for ambulant and non-ambulant patients, withand without use of steroids.[47] The scale is awaiting regulatory acceptance.

Studies have been done with neurodevelopmental scalesin young boys with Duchenne muscular dystrophy, evenfrom the neonatal period.[48–50] Findings show that these boys have delayed motor milestones, most strikingly in thegross locomotor and language subscales, and that the gapwith age-matched peers increases with age for motor skills. This result has led to the understanding among stakeholders that, should therapeutic interventions be proven effective and safe, it would be important to administer them as early as possible.

Biomarkers and surrogate endpoints

Biomarkers are important to inform and guide medicinedevelopment, and they have regulatory applications—eg, to confirm the mechanism of action (pharmacodynamicsbiomarkers). When a clear relation with clinical outcomes has been established, biomarkers can even be used as primary outcome measures (surrogate endpoints) instead of a functional outcome measure. Because biomarkers are measured objectively they are less prone to variation from factors such as motivation and compliance with functional tests. However, to fit with regulatory requirements, biomarkers must be validatedfor a specific context of use—eg, trial enrichment or surrogate endpoint. A dedicated procedure is in place atthe EMA for qualification of biomarkers and novel methods to use in the context of research and the development of drugs.[51,52]

Dystrophin

Production of dystrophin protein was deemed an obvious choice for a pharmacodynamics marker in trials of a compound aimed at re-expression of dystrophin.[53] Moreover, detection of dystrophin was a secondary endpoint in early-phase dose-escalation studies of exon skipping treatments and ataluren.[54–58] In practice, however, quantification of dystrophin is not straight- forward.[53] To use dystrophin as a pharmacodynamics biomarker,methods to quantify dystrophin must be proven reliableand reproducible. Efforts of an international working group have shown that, by using a carefully devisedstandard operating procedure, and by sharing (in a blinded fashion) the same material, patients with different levels of dystrophin production can be stratified accurately, with good intralaboratory and interlaboratory reliability and with high correlation between western blot and immunocytochemistry,[59] using several dystrophin quantification protocols.[60–62] Further improvements todecrease the coefficients of variation (particularly for low dystrophin levels) for these techniques are an important next step in validating dystrophin as a pharmacodynamics biomarker for therapeutic efficacy. Up to now, data have been insufficient to establish a clear correlation between dystrophin levels and muscle function for various stages of disease. Thus, use of dystrophin as asurrogate primary endpoint is questionable.

MRI

Techniques in MRI and magnetic resonance spectroscopy are promising for quantification of disease pathology and progression in a non-invasive and longitudinal fashion. Protocols have been developed and validated on several different magnetic resonance platforms to measure muscle oedema and inflammation in Duchenne muscular dystrophy.[63–66] Now that protocols are validated across platforms and sites, MRI and magnetic resonance spectroscopy can be used as quantitative—and in most cases exploratory—outcome measures in several ongoingnatural history studies and intervention trials. Specialisedprotocols to assess treatment effects quantitatively havebeen tested independently across neuromuscular centresworldwide, and promising results have been published.[63–67]The ImagingDMD consortium in the USA, which is supported by various patients' organisations and the USNational Institutes of Health, has collected longitudinaldata for a large cohort of patients with Duchennemuscular dystrophy. Their findings show that magneticresonance measures of T2 and lipid fraction have goodsensitivity to detect Duchenne muscular dystrophydisease pathology and progression, even in young boys inwhom functional outcomes improve with time.[68]Furthermore, MRI and magnetic resonance spectroscopycan detect the therapeutic effects of corticosteroids in reducing inflammatory processes in skeletal muscles ofboys with Duchenne muscular dystrophy.[69] As such, MRIshows promise as a surrogate outcome measure, although more data for natural history need to be collected.

Extrapolation

Because of the effect of disease stage and age on functional outcome measures for Duchenne muscular dystrophy, having well defined and homogeneous cohorts of patients in clinical trials is important. This cohort specificity can reduce patients' variability in function, which is crucial for reliable identification of a treatment effect in a specific population. However, it can also affect the indication for which the drug canpotentially be approved, because sufficient evidence needs to be available to allow for a separate risk–benefitratio conclusion in other subgroups of patients (eg, per disease stage, or ambulant *vs* non-ambulant).

Up to now, most trials in Duchenne muscular dystrophy have been done in patients who can comply with the 6MWT—ie, ambulant individuals aged 5 years and older (about 20–25% of patients). However, early treatment is anticipated to lead to a larger therapeutic effect. Nevertheless, non-ambulant patients would certainly also benefit from slower deterioration of their residual muscle function (ie, motor, respiratory, and cardiac) and, therefore, a drug indication for both ambulant and non-ambulant individuals would be a preferable goal.

Extrapolation of data from a trial done in a specific subgroup of patients to a different population should bediscussed with regulators on a case-by-case basis. The current position of the EMA is that, if supported by the mechanism of action, extrapolation of data from older toyounger (or from younger to older) patients might be discussed in the context of additional real-life data needed to be collected after authorisation. When data are generated in a subset of the population, to obtain a broadlicense for a product, further data will be needed inpatients outside this subset to address any uncertainties These aspects are discussed increasingly but, for furtherconsideration by a committee for human medicinal products (CHMP), scientific advice should be sought to discuss the most appropriate strategy for development.

Future perspectives

Since their first meeting with European regulators in 2009,[3] the academic and patient communities in Duchenne muscular dystrophy have become more aware of regulatory processes. In collaboration withpharmaceutical companies working in the area ofDuchenne muscular dystrophy, these stakeholders havetried to address gaps in knowledge identified during themeeting.[70] Large amounts of data have been collected and new outcome measures and tools have beendeveloped,

building on existing resources—eg, patient registries—provided by patients' organisations and TREAT-NMD.[6,71–73] At the same time, regulators have become more familiar with the specifics of developing new medicines for Duchenne muscular dystrophy and have finalised guidelines on product development for Duchenne and Becker muscular dystrophies.[4] This improved mutual understanding has been helpful for a continuous and constructive dialogue that has moved the area forward. A stakeholder meeting held in April, 2015, in London, UK, allowed for further alignment of ongoing work and prioritisation of future efforts.

First, efforts to increase international awareness of care standards for Duchenne muscular dystrophy need to continue, because patients deserve access to optimum care. Plans to set up a European Reference Network for neuromuscular disorders will build on the TREAT-NMD care and trial site registry (CTSR)[72] and the CARE-NMD project[19] and facilitate implementation of care standards for Duchenne muscular dystrophy throughout Europe. This work would complement efforts Parent Project Muscular Dystrophy (PPMD) is currently coordinating in the USA to certify centres that provide care according to international guidelines.[74]

Second, new centres participating in trials are needed. Many clinical trials are currently done in the area of Duchenne muscular dystrophy, resulting in capacity problems at experienced trial sites. Adhering to care standards is a prerequisite to be selected as a trial site by pharmaceutical companies.

Third, another PPMD-led initiative is defining core sets of outcome measures to be used in ambulant and non- ambulant patients, which ideally should be used in all trials for Duchenne muscular dystrophy. This stand- ardisation would facilitate the trial process, because personnel will have to be trained once rather than for every trial. Furthermore, it would allow comparison of results between different trials and facilitate post- marketing surveillance.

Fourth, regulators offer scientific and regulatory guidance. Platforms are available to discuss specific medicine development, development of biomarkers, functional outcome measures, and patient-reported outcomes, for example. Through increased dialogue, advice can be sought from the EMA towards qualifi-cation of outcome measures in Duchenne muscular dystrophy—eg, the Performance of Upper Limb scale as a functional outcome measure in non-ambulant patients, and MRI as a biomarker or surrogate endpoint for Duchenne muscular dystrophy. The same platform could be considered for the quantification of dystrophin expression as a pharmacodynamic biomarker, which has been discussed at a workshop organised by the FDA and the National Institutes of Health.[75]

Fifth, developing a treatment for a rare disease such as Duchenne muscular dystrophy should be a global effort. Regulatory requirements should be aligned and commun-ication should be continuous between regulatory bodies in different global regions with respect to guidelines for treatment development and biomarker qualification.[76]

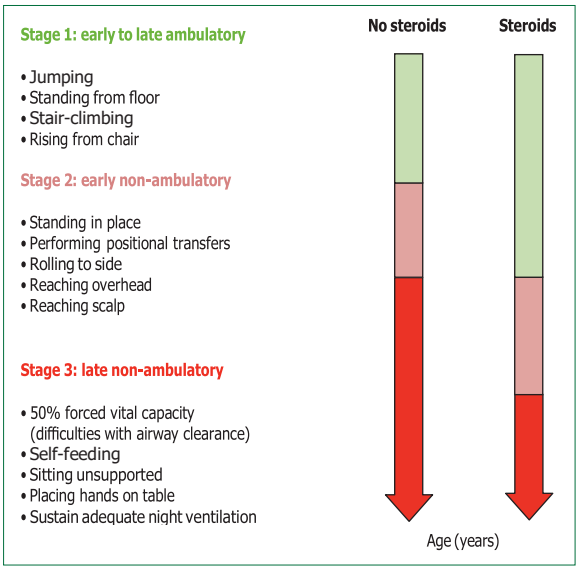
Sixth, publication of data in peer-reviewed journals is important, because this process informs the scientific community and regulatory bodies, allowing data to be used in guideline development, scientific advice, and medicine assessment. Data have been published for natural history and functional outcome measures in ambulant patients, and researchers have started publishing data for MRI as a potential biomarker for muscle quality. Focus should now be on producing natural history data and outcome measures for non-ambulant patients—eg, upper-limb function scales and heart and respiratory function.

Seventh, placebo-controlled trials are needed to study safety and efficacy of new treatments. However, future use of natural history data or data from the placebo arm of other trials has not been excluded. Several large, natural history studies are underway (eg, NCT01753804, NCT01385917, and NCT00468832): it is important to align the outcome measures used in ongoing natural history studies and clinical trials and for the research groups involved to share their datasets. Several initiatives to collect and curate datasets are ongoing.

Finally, most clinical trials are done in selected populations of patients with Duchenne muscular dystrophy, generally in ambulant patients. However, to allow extrapolation of efficacy and safety data to obtain a broader indication (eg, for all patients with Duchenne muscular dystrophy rather than a focus on a specific group of ambulant boys), collection of data to validate the extrapolation is crucial. Data obtained in patients outside the inclusion criteria of the trial population are needed; collection of natural history data and development of outcome measures will be increasingly important, as well as for effective assessments in post-marketing studies.

Concluding remarks

The collaborative effort of researchers, health-care professionals, representatives from industry, regulators, and patients has been instrumental in moving the area of Duchenne muscular dystrophy forward in Europe (panel 4). In parallel, comparable efforts are ongoing in the USA (eg, the Action Plan for Muscular Dystrophies),[77,78] and the FDA has programmes for clinical outcome assessment, biomarker qualification, and regulatory guidance.[79–81] Nevertheless, the work is not yet complete and eight new focus areas have been identified. Each of these priority areas will need continued involvement from stakeholders. Although these tasks might seem challenging, a strong basis of previous work, mutual understanding, and collabor- ation will aid these efforts. Previous work focused mainly on doing trials to obtain marketing authorisation; however, research has now started to address challenges around post-marketing and treatment access strategies.



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