for patients with ≥6 months of follow-up (N=73). The NNT to prevent one death, one event (death or use of permanent assisted ventilation), or for one patient to improve motor function relative to nusinersen was calculated as the reciprocal of the difference between AVXS-101 and nusinersen in event rates or motor function achievement rates. Patient mean age at first dose was 3.4 (0.9-7.9) and 5.3 (1.7-7.9) months in the AVXS-101 and nusinersen trials. NNT analyses suggests that treating 6.2 patients with AVXS-101 instead of nusinersen would prevent 1 more death by the last visit; treating 2.6 patients with AVXS-101 versus nusinersen would prevent 1 more event; and treating 3.5 patients with AVXS-101 versus nusinersen would allow 1 more patient to improve motor function (at last visit and at a median of 9 months). Efficacy in preventing death and use of permanent assisted ventilation and in improving motor function is much higher with AVXS-101 versus nusinersen.

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**P.97**

**Development of a decision-analytic model for the economic evaluation of newborn screening for spinal muscular atrophy**

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Economic considerations are increasingly important to help decision makers to efficiently allocate health care resources. To date, very little information is available on the cost-effectiveness of spinal muscular atrophy (SMA) treatment and newborn screening; yet more and more screening programs are being implemented in the USA and in Europe. The aim of this study is therefore to develop a decision-analytic model to assess the cost-effectiveness of newborn screening and pre-symptomatic treatment of SMA as compared to post-symptomatic treatment. Newborn screening for SMA has started since Marsh 05th in Southern Belgium. We are developing a decision-analytic model in Excel with a lifetime horizon and a societal perspective. This model includes events (such as death, permanent ventilation, etc), transition, utilities, and costs. Data was retrieved from literature reviews, available non-published data from Nurture, and data collected from the European Natural History Study in SMA. We also collected data from the large post symptomatic treated cohort of Liege, Belgium. All such data was acquired in centers applying updated standards of care. The quality of life of patients and parents was included in the analysis, as well as the productivity losses of parents. The model thus estimates the costs and effects (expressed in quality-adjusted life years) of newborn screening and to compare it with a situation where all patients are diagnosed post-symptomatically. Initial data suggests promising results and reveal key factors on the cost-effectiveness of NBS. The model requires adjustment to be fully validated.

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## LGMD AUTOSOMAL RESSESSIVE AND DOMINANT

**P.98**

**AAV-mediated gene transfer of FKRP for therapy of LGMD2I**

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Dystroglycanopathies constitute a group of genetic diseases caused by defective glycosylation of alpha-dystroglycan $\alpha$, a membrane glycoprotein involved in the cell/matrix anchoring of muscle fibers. The aDG glycosylation, a very complex process, requires many proteins whose functions are not fully elucidated. In particular, mutations in the *FKRP* gene encoding Fukutin related protein lead to hypoglycosylation of $\alpha$, resulting in different forms of dystroglycanopathies, among which Limb Girdle Muscular Dystrophy type 2I (LGMD2I). We and others have published the proof of concept of *FKRP* gene transfer using an AAV vector for treating FKRP deficiencies. As the knock-in mouse models used in these studies are not severe enough to evaluate properly the dose-effect of AAV-FKRP administration, we developed a muscle specific FKRP knock-down mouse model. This new mouse model, named HSA-FKRPdel, presents a much more severe phenotype than observed in knock-in mouse. Defects of glycosylation of $\alpha$DG and of its binding to laminin were observed, as well as histological dystrophic signs as centronucleation and inflammation. Functional evaluation also showed a reduced force of HSA-FKRPdel mice. AAV-*FKRP* was systemically administrated to this new mouse model at different doses. Depending of the dose, positive effects were observed at the molecular, histological and functional levels. Full animal characterization and therapeutic effects will be presented. Development of AAV production at the GMP level is now on going. These data will be included in an IND for AAV-mediated transfer of FKRP in patients.

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**P.99**

**Limb-girdle muscular dystrophy 2Z in a Bulgarian family**

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Mutations in *POGLUT1* (protein O-glucosyltransferase 1), an enzyme involved in Notch posttranslational modification and function have been recently identified as causing a new type of limb-girdle muscular dystrophy, known as LGMD2Z. The clinical features of the identified patients encompassed variable clinical onset from 1st to 5th decade, muscle weakness predominantly in the proximal lower limbs, followed by upper limb involvement and wheelchair confinement. We report a Bulgarian family with three affected sisters, homozygous for R98W mutation in *POGLUT1*. They underwent neurological examination, electromyography, measurement of creatine kinase, ventilatory assessment, electrocardiography, echocardiography and muscle muscle magnetic resonance imaging (MRI). The initial complaints in two of them were noticed at the age of 24-25 years, while in the third- at the age of 44 years. The leading symptoms at onset were muscle weakness in the proximal leg muscles with difficulties in climbing stairs and getting up from squatting position. The involvement of the upper limbs was noticed between 6 and 23 years after the lower limb weakness. CK was within normal range in all three affected. The cardiac function seamed spared, mild restrictive respiratory involvement was observed in only one of the sisters. MRI of the legs revealed early fatty replacement of internal regions of thigh muscles and sparing of the external areas. In conclusion *POGLUT1* mutations are associated with late onset AR LGMD with specific MRI pattern of inside-to-outside mode of fatty degeneration in the lower limbs.

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**P.100**

***BVES* loss-of-function mutations in limb-girdle muscular dystrophy 2X with cardiac conduction disorders**

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*BVES* encodes for a 360 amino acid protein also known as POPDC1, which is part of the Popeye domain containing (POPDC) family of proteins. POPDC1, POPDC2 and POPDC3 are cAMP-binding transmembrane proteins that are abundantly expressed in striated muscle. A homozygous