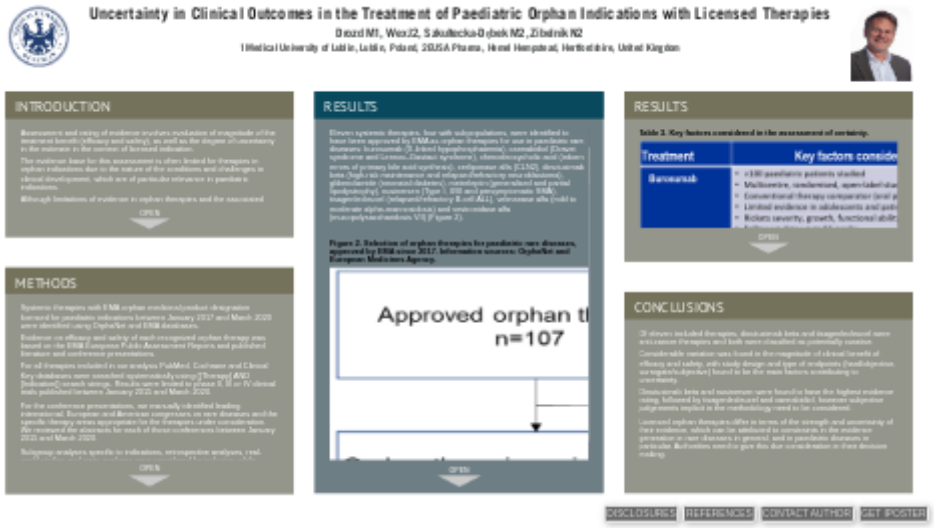
Uncertainty in Clinical Outcomes in the Treatment of Paediatric Orphan Indications with Licensed Therapies



Drozd M1, Wex J2, Szkultecka-Dębek M2, Zibelnik N2

1Medical University of Lublin, Lublin, Poland, 2EUSA Pharma, Hemel Hempstead, Hertfordshire, United Kingdom

PRESENTED AT:

INTRODUCTION

Assessment and rating of evidence involves evaluation of magnitude of the treatment benefit (efficacy and safety), as well as the degree of uncertainty in the estimate in the context of licensed indication.

The evidence base for this assessment is often limited for therapies in orphan indications due to the nature of the conditions and challenges in clinical development, which are of particular relevance in paediatric indications.

Although limitations of evidence in orphan therapies and the associated uncertainty are widely acknowledged in clinical decision making and accepted by payers, the factors contributing to uncertainty and its variation across therapies warrants comparative analysis.

Despite existence of numerous frameworks for the evaluation and rating of evidence, none have been identified to be specifically designed for addressing both clinical benefit and uncertainty in orphan therapies.

We aimed to explore uncertainty, focusing on clinical outcomes in the treatment of paediatric rare diseases to inform clinical and payer decision making.

METHODS

Systemic therapies with EMA orphan medicinal product designation licensed for paediatric indications between January 2017 and March 2020 were identified using OrphaNet and EMA databases.

Evidence on efficacy and safety of each recognized orphan therapy was based on the EMA European Public Assessment Reports and published literature and conference presentations.

For all therapies included in our analysis PubMed, Cochrane and Clinical Key databases were searched systematically using ([Therapy] AND [Indication]) search strings. Results were limited to phase II, III or IV clinical trials published between January 2015 and March 2020.

For the conference presentations, we manually identified leading international, European and American congresses on rare diseases and the specific therapy areas appropriate for the therapies under consideration. We reviewed the abstracts for each of those conferences between January 2015 and March 2020.

Subgroup analyses specific to indications, retrospective analyses, real-world studies and meta-analyses were considered for inclusion, while phase I data, preclinical research and case reports were excluded.

We extracted clinical data on each therapy under the PICOS headings: population (where the approved indication was not restricted to children, we focused on clinical trials including patients ≤18 years), intervention, comparator (as used in clinical trials), outcomes (primary efficacy outcomes, clinically relevant secondary efficacy outcomes, and safety) and study design.

Benefit-risk and degree of uncertainty associated with each therapy were rated using Evidence Rating Matrix for Comparative Clinical Effectiveness developed by the Institute for Clinical and Economic Review (ICER). The ICER Matrix captures the magnitude of the difference between a therapeutic agent and its comparator in terms of Comparative Net Health Benefit, which is the balance between clinical benefits and risks or adverse effects as negative, comparable, small or substantial. The level of certainty in the estimate of the Comparative Net Health Benefit is defined in the ICER Matrix is as low, moderate or high.

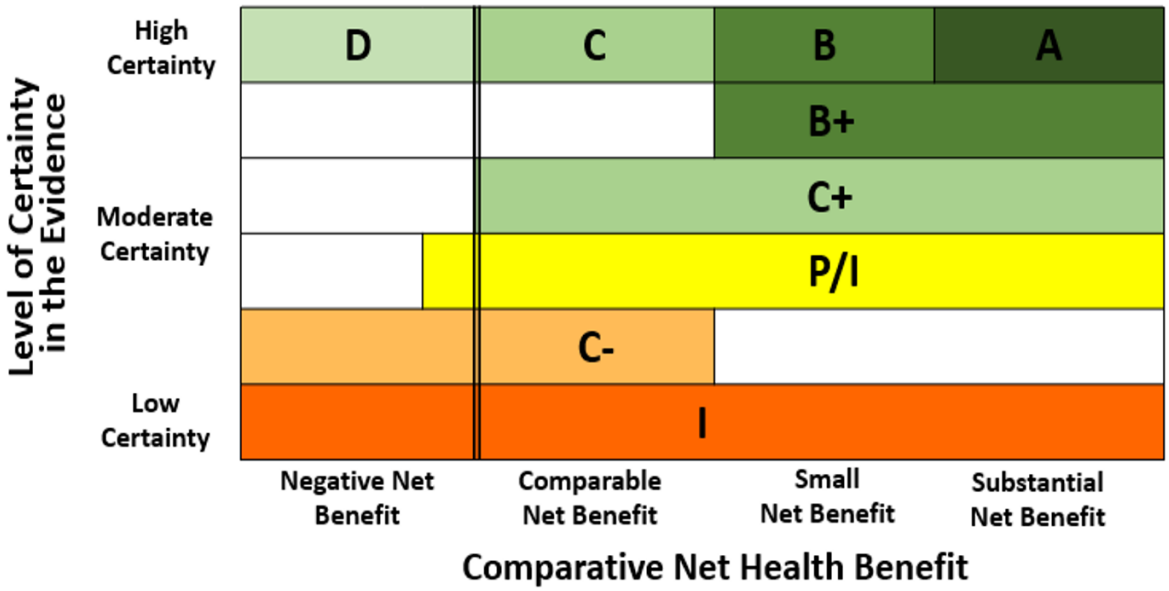
Magnitude of comparative Net Health Benefit (NHB) was assessed using the ESMO-Magnitude of Clinical Benefit Scale for anti-cancer therapies, separately for likely curative and likely non-curative therapies. For other therapies the magnitude of the treatment effects was considered along with frequency of Grade 3 and 4 adverse events with 30% cut-off.

Uncertainty was assessed based the strength of evidence, accounting for risk of bias, generalizability of trial population to the population within licensed indication, precision of the estimates of outcomes, consistency between studies, directness of the comparison and type of efficacy outcomes (hard or surrogate).

To further explore uncertainty associated with each treatment, the duration of each treatment was estimated based on EMA Summary of Product Characteristics and dosing reported in clinical trials. Treatments were categorised as having defined and undefined duration.

The evidence was rated by all authors by assigning by consensus the categories along the dimensions of comparative Net Health Benefit and Level of Certainty in the Evidence in the ICER Evidence Rating Matrix (Fig. 1).

Figure 1. Evidence Rating Matrix for Comparative Clinical Effectiveness developed by the Institute for Clinical and Economic Review (ICER).

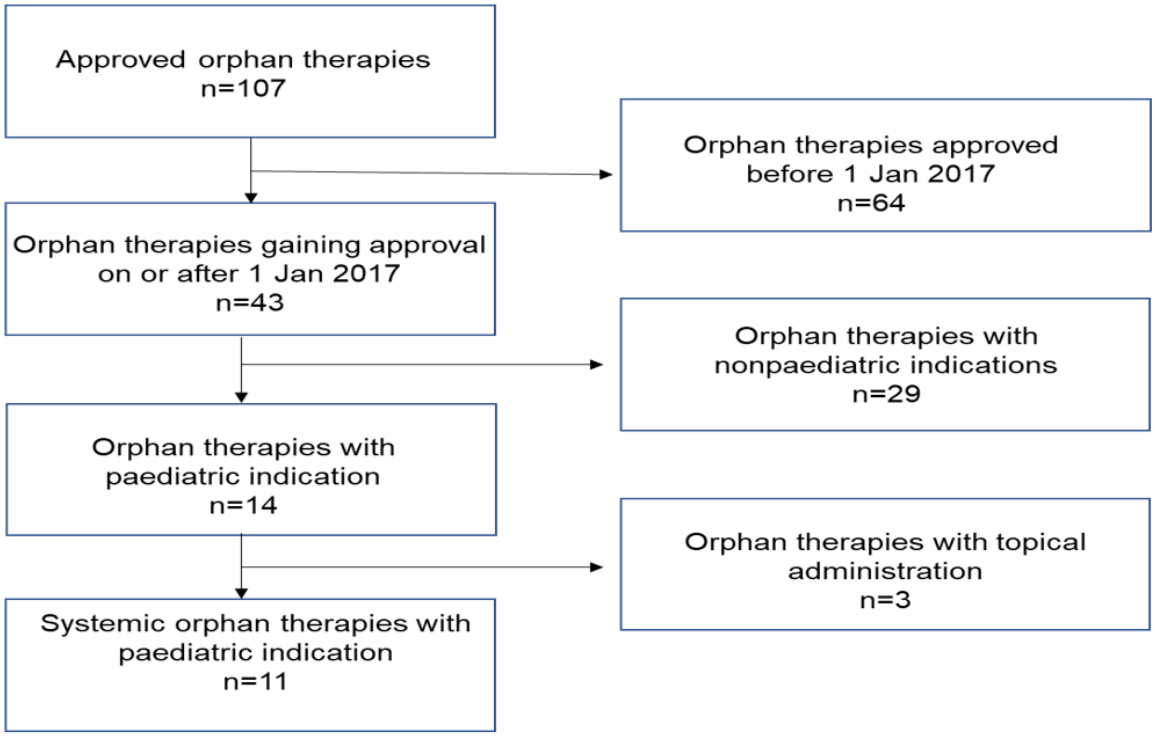


Source: https://icer.org/evidence-rating-matrix (https://icer.org/evidence-rating-matrix/)

RESULTS

Eleven systemic therapies, four with subpopulations, were identified to have been approved by EMA as orphan therapies for use in paediatric rare diseases: burosumab (X-linked hypophosphatemia), cannabidiol (Dravet syndrome and Lennox–Gastaut syndrome), chenodeoxycholic acid (inborn errors of primary bile acid synthesis), cerliponase alfa (CLN2), dinutuximab beta (high-risk maintenance and relapsed/refractory neuroblastoma), glibenclamide (neonatal diabetes), metreleptin (generalised and partial lipodystrophy), nusinersen (Type I, II/III and presymptomatic SMA), tisagenlecleucel (relapsed/refractory B-cell ALL), velmanase alfa (mild to moderate alpha-mannosidosis) and vestronidase alfa (mucopolysaccharidosis VII) (Figure 2).

Figure 2. Selection of orphan therapies for paediatric rare diseases, approved by EMA since 2017. Information sources: OrphaNet and European Medicines Agency.



The literature search identified total of 1,353 items for all 11 treatments, of which 114 with 40 studies reported (Table 1) were included in the analysis.

Table 1. Results of the literature search for each of the identified therapies.

Sources searched	Total Results	PubMed	Clinical Key	Cochrane	Conferences	Results Included	Studies Included
Burosumab	109	33	0	2	74	10	3 [1-3]
Cannabidiol	372	81	127	45	119	22	6 [4-10]
CDCA	63	20	23	11	9	4	5 [11-15]
Cerliponase alfa	34	8	1	0	25	7	2 [16-17]
Dinutuximab beta	75	14	10	0	51	10	3 [18-25]
Glibenclamide	112	40	18	31	23	2	4 [26-29]
Metreleptin	91	33	21	22	15	6	3 [30-32]
Nusinersen	261	148	2	2	109	17	6 [33-41]
Tisagenlecleucel	188	51	2	55	80	18	3 [42-44]
Velmanase alfa	27	6	0	0	21	14	2 [45-49]
Vestronidase alfa	21	6	4	2	9	4	3 [50-52]

Of the 11 identified therapies, two were anti-cancer therapies, and their NHB was assessed using ESMO-MCBS scales as 4/A for dinutuximab beta and 2 for tisagenlecleucel. Those two therapies were classified as potentially curative.

Burosumab, cannabidiol, glibenclamide, metreleptin, nusinersen, velmanase alfa and vestronidase alfa had frequency of adverse events <30%.

NHB was the highest (substantial) for dinutuximab beta in the maintenance population and nusinersen in Type I SMA (Table 2).

Table 2. Net health benefit, certainty and ICER rating results.

Treatment	Net Health Benefit [ESMO-MCBS]	Potentially Curative?	Grade 3-4 AEs <30%	Certainty	ICER Rating
Burosumab	Comparable/Small	-	+	Moderate	C+
Cannabidiol DS	Small/Substantial	-	+	Moderate	B+
Cannabidiol LGS	Small/Substantial	-	+	Moderate	B+
Chenodeoxycholic acid (CDCA)	Comparable/Small	-	NR	Low	I
Cerliponase alpha	Comparable/Small	-	- (Control NR)	Moderate	C+
Dinutuximab beta Maintenance	Substantial [ESMO 1:A; 2A:4]	+	-	High	A
Dinutuximab beta Relapsed/Refractory	Small/Substantial [ESMO 2A:4; 1:A]	+	-	Moderate	B+
Glibenclamide	Comparable/Small	-	+	Moderate	C+
Metreleptin generalised lipodystrophy	Comparable/Small	-	+	Moderate	C+
Metreleptin partial lipodystrophy	Comparable/Small	-	+	Low	I
Nusinersen Type I	Substantial	-	+	High	A
Nusinersen Type II/III	Small/Substantial	-	+	Moderate	B+
Nusinersen Type presymptomatic	Small/Substantial	-	+	Moderate	B+
Tisagenlecleucel	Small/Substantial [ESMO 2:2]	+	-	Moderate	B+
Velmanase alfa	Comparable/Small	-	+	Moderate	C+
Vestronidase alfa	Comparable/Small	-	+	Low	I

Uncertainty in identified evidence was associated with all aspects of the PICOS framework: the treated population, intervention, comparator, outcomes and study design (Table 3).

Most therapies were associated with moderate certainty, with dinutuximab beta in maintenance population and nusinersen in Type I SMA assigned high certainty, and CDCA, metreleptin in partial lipodystrophy and vestronidase alfa – with low certainty.

The ICER Evidence Matrix rating was A, B+, C+ or I (Table 2).

RESULTS

Table 3. Key factors considered in the assessment of certainty.

Treatment	Key factors considered in certainty assessment
Burosumab	• >100 paediatric patients studied • Multicentre, randomised, open-label studies; multicentre single-arm study • Conventional therapy comparator (oral phosphates and active Vitamin D analogues) • Limited evidence in adolescents and patients with milder severity • Rickets severity, growth, functional ability, pain outcomes • Follow up data up to 64 weeks • Different dosing across studies, undefined treatment duration, potentially lifelong treatment
Cannabidiol	• >1,000 patients studied, including adults • Multicentre, randomised, double-blind, placebo-controlled controlled studies; open label extensions • Variation in conventional clinical management • Unknown relationship between reduced seizure frequency and overall survival • Quality of life outcomes, including patient and carer-reported • Follow-up data up to 3 years • Dosing based on individual clinical response with undefined treatment duration, potentially lifelong
CDCA	• >150 patients studied, including adults • Multicentre and single centre retrospective studies • Comparative data from literature • Patient populations with different symptoms/disability, disease duration and treatment duration • Metabolic outcomes, clinical symptoms, quality of life, disability scores • Median follow-up >8 years • Dosing adjusted individually with undefined treatment duration, potentially lifelong (replacement therapy)
Cerliponase alfa	• >20 patients studied • 1 multicentre, single-arm study, natural history historical control study • Motor-language score, quality of life outcomes • Differences in definitions of symptom severity scores in treated patients and historical controls • Follow-up data up to 2 years, 1 year for historical controls • Undefined treatment duration, potentially lifelong (replacement therapy)
Dinutuximab beta	• >1,000 paediatric patients studied • Multicentre, open-label prospective study with historical control from non-concurrent randomisation of the same trial; multicentre single-arm prospective studies with historical controls • Conventional therapy comparator (non-immunotherapy) • Different populations in maintenance and relapsed/refractory • Overall survival, event-free and progression-free survival endpoints • Follow-up data up to 7 years • Defined dose and treatment duration (limited to 5 cycles); 5-day or 10-day infusion regimens
Glibenclamide	• >150 paediatric patients studied • Multicentre single-arm and single-centre single-arm prospective studies • Lack of comparative effectiveness data; established evidence base in other types of diabetes (different formulations) • Withdrawal of insulin therapy, glycaemic control, neuro-psychomotor outcomes, acceptability of the oral suspension formulation • Median follow-up >10 years • Undefined treatment duration, potentially lifelong
Metreleptin	• >200 patients studied, including adults • Multicentre, single-arm and single-centre single arm prospective studies; multicentre retrospective study • Heterogeneous population comprising various types of lipodystrophy • Glycaemic control, metabolic outcomes • Follow-up over 14 years • Dose adjustment based on response to treatment, undefined treatment duration, potentially lifelong
Nusinersen	• >500 paediatric patients studied • Multicentre, randomised, double-blind, sham-controlled studies; multicentre, single-arm open label study • Differences in SMA subtype populations • Motor function, event-free survival, overall survival outcomes • Follow-up over 6 years • Undefined treatment duration, potentially lifelong, different dosing across trials
Tisagenlecleucel	• >250 patients studied, including adults • Multicentre and single-centre single-arm studies • Unadjusted/naïve comparisons to comparator therapies • Response rates, event-free survival, overall survival, quality of life outcomes • Follow-up over 3 years • One-time treatment; different numbers of infusions in trials; lag time to prepare engineered cells potentially affecting eligibility
Velmanase alfa	• >50 patients studied, including adults • Multicentre, double-blind, placebo-controlled study; "integrated database" including several small single-arm cohort studies • Heterogeneity in severity of the disease of included patients • Metabolic, functional and quality of life outcomes

	• Metabolic, functional and quality of life outcomes • Follow-up up to 48 months • Undefined treatment duration, potentially lifelong
Vestronidase alfa	• >25 patients studied • Multicentre, blind-start, single crossover, placebo-controlled study; multicentre, single-arm study • Metabolic, functional and quality of life outcomes • Heterogeneity in severity of the disease of included patients • Follow-up up to 48 weeks (extension ongoing) • Unclear optimal treatment duration

CONCLUSIONS

Of eleven included therapies, dinutuximab beta and tisagenlecleucel were anti-cancer therapies and both were classified as potentially curative.

Considerable variation was found in the magnitude of clinical benefit of efficacy and safety, with study design and type of endpoints (hard/objective, surrogate/subjective) found to be the main factors contributing to uncertainty.

Dinutuximab beta and nusinersen were found to have the highest evidence rating, followed by tisagenlecleucel and cannabidiol, however subjective judgements implicit in the methodology need to be considered.

Licensed orphan therapies differ in terms of the strength and uncertainty of their evidence, which can be attributed to constraints in the evidence generation in rare diseases in general, and in paediatric diseases in particular. Authorities need to give this due consideration in their decision making.

DISCLOSURES

EUSA Pharma financially sponsored this project and participated in the interpretation of results, writing, review and approval of the abstract and poster.

J Wex, M Szkultecka-Dębek and N Zibelnik are employees of EUSA Pharma.

REFERENCES

1. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. Lancet. 2019;393(10189):2416-2427.

2. Carpenter TO, Högler W, Imel EA, et al. Continued improvement in clinical outcomes with long-term burosumab, a fully human anti-FGF23 monoclonal antibody: results from a 3-year, phase 2, clinical trial in children with X-linked hypophosphatemia (XLH). J Bone Miner Res. 2019;34:Abstract 1037.

3. Whyte MP, Carpenter TO, Gottesman GS, et al. Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. Lancet Diabetes Endocrinol. 2019;7(3):189-199.

4. Devinsky O, Cross JH, Laux L, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017;376(21):2011-2020.

5. Miller I, Scheffer IE, Gunning B, et al. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol. 2020;77(5):613-621.

6. Halford JJ, Scheffer I, Nabbout R, et al. Long-term safety and efficacy of cannabidiol (CBD) treatment in patients with Dravet syndrome (DS): 3-year interim results of an open-label extension (OLE) trial (GWPCARE5). Neurology. 2020;94:Abstract 439.

7. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med. 2018;378(20):1888-1897.

8. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085-1096.

9. Patel A, Chin R, Mitchell W, et al. Long-term safety and efficacy of cannabidiol (CBD) treatment in patients with Lennox Gastaut syndrome (LGS): 3-year results of an open-label extension (OLE) trial (GWPCARE5). Neurology. 2020;94:Abstract 668.

10. Laux LC, Bebin EM, Checketts D, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. Epilepsy Res. 2019;154:13-20.

11. Zübarioğlu T, Bilen İ P, Kıykım E, et al. Evaluation of the effect of chenodeoxycholic acid treatment on skeletal system findings in patients with cerebrotendinous xanthomatosis. Turk Pediatri Ars. 2019;54(2):113-118.

12. Stelten BML, Huidekoper HH, van de Warrenburg BPC, et al. Long-term treatment effect in cerebrotendinous xanthomatosis depends on age at treatment start. Neurology. 2019;92(2):e83-e95.

13. Verrips A, Dotti MT, Mignarri A, Stelten BML, Verma S, Federico A. The safety and effectiveness of chenodeoxycholic acid treatment in patients with cerebrotendinous xanthomatosis: two retrospective cohort studies. Neurol Sci. 2020;41(4):943-949.

14. Amador MDM, Masingue M, Debs R, et al. Treatment with chenodeoxycholic acid in cerebrotendinous xanthomatosis: clinical, neurophysiological, and quantitative brain structural outcomes. J Inherit Metab Dis. 2018;41(5):799-807.

15. Duell PB, Salen G, Eichler FS, et al. Diagnosis, treatment, and clinical outcomes in 43 cases with cerebrotendinous xanthomatosis. J Clin Lipidol. 2018;12(5):1169-1178.

16. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report: Brineura (EMEA/H/C/004065/0000). https://www.ema.europa.eu/en/medicines/human/EPAR/brineura. Published 2017. Accessed 03 August 2020.

17. Schulz A, Ajayi T, Specchio N, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. N Engl J Med. 2018;378(20):1898-1907.

18. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report: Qarziba (EMEA/H/C/003918/0000). https://www.ema.europa.eu/en/medicines/human/EPAR/qarziba. Published 2017. Accessed 03 August 2020.

19. Ladenstein R, Pötschger U, Valteau-Couanet D, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(12):1617-1629.

20. Ladenstein R, Pötschger U, Valteau-Couanet D, et al. Investigation of the Role of Dinutuximab Beta-Based Immunotherapy in the SIOPEN High-Risk Neuroblastoma 1 Trial (HR-NBL1). Cancers (Basel). 2020;12(2).

21. Lode H, Jensen C, Siebert N, et al. Abstract CT410: Immune activation, clinical response and survival following long-term infusion of anti-GD2 antibody ch14.18/CHO in combination with interleukin-2 in high-risk neuroblastoma patients. Cancer Research. 2014;74(19 Supplement):CT410-CT410.

22. Lode HN, Valteau-Couanet D, Gray J, et al. Randomized use of anti-GD2 antibody dinutuximab beta (DB) long-term infusion with and without subcutaneous interleukin-2 (scIL-2) in high-risk neuroblastoma patients with relapsed and refractory disease: Results from the SIOPEN LTI-trial. In: American Society of Clinical Oncology; 2019.

23. Siebert N, Troschke-Meurer S, Marx M, et al. Impact of HACA on Immunomodulation and Treatment Toxicity Following ch14.18/CHO Long-Term Infusion with Interleukin-2: Results from a SIOPEN Phase 2 Trial. Cancers (Basel). 2018;10(10).

24. Mueller I, Ehlert K, Endres S, et al. Tolerability, response and outcome of high-risk neuroblastoma patients treated with long-term infusion of anti-GD(2) antibody ch14.18/CHO. MAbs. 2018;10(1):55-61.

25. Wex J, Zibelnik N, Zemam A. Dinutuximab beta with isotretinoin versus isotretinoin alone in the treatment of high-risk neuroblastoma: impact on long-term survival. Value Health. 2019;22:S435 (abstract PCN434).

26. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006;355(5):467-477.

27. Beltrand J, Elie C, Busiah K, et al. Sulfonylurea Therapy Benefits Neurological and Psychomotor Functions in Patients With Neonatal Diabetes Owing to Potassium Channel Mutations. Diabetes Care. 2015;38(11):2033-2041.

28. Beltrand J, Baptiste A, Busiah K, et al. Glibenclamide oral suspension: Suitable and effective in patients with neonatal diabetes. Pediatr Diabetes. 2019;20(3):246-254.

29. Bowman P, Sulen Å, Barbetti F, et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. Lancet Diabetes Endocrinol. 2018;6(8):637-646.

30. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report: Myalepta (EMEA/H/C/004218/0000). https://www.ema.europa.eu/en/medicines/human/EPAR/myalepta. Published 2018. Accessed 03 August 2020.

31. Brown RJ, Oral EA, Cochran E, et al. Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy. Endocrine. 2018;60(3):479-489.

32. Cook K, Stears A, Araujo-Vilar D, et al. Real-world experience of generalized and partial lipodystrophy patients enrolled in the metreleptin early access program. Paper presented at: 21st European Congress of Endocrinology2019.

33. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report: Spinraza (EMEA/H/C/004312/0000). https://www.ema.europa.eu/en/medicines/human/EPAR/spinraza. Published 2017. Accessed 04 December 2020.

34. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017;377(18):1723-1732.

35. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Spinraza -H-C-004312-P46-007: EPAR - Assessment Report. Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006. https://www.ema.europa.eu/en/documents/variation-report/spinraza-h-c-004312-p46-007-epar-assessment-report_en.pdf. Published 2018. Accessed 04 December 2020.

36. Castro D, Finkel RS, Farrar MA, et al. Nusinersen in infantile-onset spinal muscular atrophy: results from longer-term treatment from the open-label SHINE extension study. Neurology. 2020;94:S12.008.

37. Darras BT, De Vivo DC, Farrar MA, et al. Safety Profile of Nusinersen in Presymptomatic and Infantile-Onset Spinal Muscular Atrophy (SMA): Interim Results From the NURTURE and ENDEAR-SHINE Studies (1659). Neurology. 2020;94(15 Supplement):1659.

38. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med. 2018;378(7):625-635.

39. Shieh PB, Acsadi G, Mueller-Felber W, et al. Safety and efficacy of nusinersen in infants/children with spinal muscular atrophy (SMA): part 1 of the phase 2 EMBRACE study. Neurology. 2018;90:P2.324.

40. Chiriboga CA, Darras BT, Farrar MA, et al. Longer-term Treatment With Nusinersen: Results in Later-onset Spinal Muscular Atrophy From the SHINE Study. Neurology. 2020;94:P6.007.

41. De Vivo DC, Bertini E, Swoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord. 2019;29(11):842-856.

42. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report: Kymriah (EMEA/H/C/004090/0000). https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah. Published 2018. Accessed 03 August 2020.

43. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-448.

44. Laetsch TW, Myers GD, Baruchel A, et al. Patient-reported quality of life after tisagenlecleucel infusion in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: a global, single-arm, phase 2 trial. Lancet Oncol. 2019;20(12):1710-1718.

45. Borgwardt L, Guffon N, Amraoui Y, et al. Efficacy and safety of Velmanase alfa in the treatment of patients with alpha-mannosidosis: results from the core and extension phase analysis of a phase III multicentre, double-blind, randomised, placebo-controlled trial. J Inherit Metab Dis. 2018;41(6):1215-1223.

46. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report: Lamzede (EMEA/H/C/003922/0000). https://www.ema.europa.eu/en/medicines/human/EPAR/lamzede. Published 2018. Accessed 03 August 2020.

47. Borgwardt L, Guffon N, Amraoui Y, et al. Health Related Quality of Life, Disability, and Pain in Alpha Mannosidosis:Long-Term Data of Enzyme Replacement Therapy With Velmanase Alfa (Human Recombinant Alpha Mannosidase). Journal of Inborn Errors of Metabolism and Screening. 2018;6:2326409818796854.

48. Lund AM, Borgwardt L, Cattaneo F, et al. Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis. J Inherit Metab Dis. 2018;41(6):1225-1233.

49. Cattaneo F, Borgwardt L, Dali C, et al. Quality of life and activities of daily living in alpha-mannosidosis: long-term data of enzyme replacement therapy with velmanase alfa (human recombinant alpha mannosidase). J Inborn Errors Metab Screen. 2016;4:60-61.

50. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report: Mepsevii (EMEA/H/C/004438/0000). https://www.ema.europa.eu/en/medicines/human/EPAR/mepsevii. Published 2018. Accessed 03 August 2020.

51. Wang RY, da Silva Franco JF, López-Valdez J, et al. The long-term safety and efficacy of vestronidase alfa, rhGUS enzyme replacement therapy, in subjects with mucopolysaccharidosis VII. Mol Genet Metab. 2020;129(3):219-227.

52. Gonzalez-Meneses Lopez AGL, Beuno MB, Lau HL, et al. P-371 Vestronidase alfa stabilizes or improves disease manifestations in subjects with MPS VII. J Inherit Metab Dis. 2018;41:S187-S188.