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Efficacy and Safety of Reimbursed Orphan Medicines in Bulgaria – Systematic Review and Meta-analysis (Part I)

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Authors' contributions

This work was carried out in collaboration between all authors. Author MK performed the systematic literature review and conceptualized the approach. Authors KM and Miglena Doneva interpreted the data, conducted meta-analysis and analyzed the results. Authors AS, Maria Dimitrova and GP interpreted the data and critically reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: To make reimbursement decisions for orphan medicines the regulators need robust evidences for their efficacy and safety provided by systematic reviews and meta-analyses.
The goal of the current study is to evaluate the efficacy and safety of orphan medicines included in the Positive Drug List (PDL) in Bulgaria through the application of meta-analysis.
Methods: Internet based literature search in scientific databases such as Pub Med, ClinicalTrials.gov, EU Clinical Trials Register for the identification of all published clinical trials with orphan medicines Idursulfase, Sapropterin and Pasireotide was performed. The technological Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was applied to present the flow of information during the different stages of systematic review. A set of

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statistical methods available in statistical software MedCalc were used to perform meta-analysis and comparison of proportions for diseases' specific clinical parameters and adverse reactions. The studies were filtered on the basis of eligibility criteria: A clinical focus; randomized or open-label studies with clearly presented outcome variables; equal or similar time horizon; sufficient data about safety and efficacy processed with reliable statistical approaches.

Results: Fixed effect was used in patients treated with Idursulfase who experienced urticaria (p = 0.3459, 6.81%, 95% CI 3,126-12,623) and serious adverse drug reactions (ADRs) (p=0.0619, 21.27%, 95% CI, 14,561 - 29,345) and in patients treated with Sapropterin who experienced ADRs (P = 0.2264, 29,237%, 95% CI 20,916-38,720). Random effect was taken into account for Pasireotide effectiveness data and the percent of patients with controlled levels of urinary free cortisol (UFC) was 44.81%, 95% CI (37,506 - 56,073), which proves the difference in the effects among different samples. The results from the heterogeneity test shows that random effect for the percent of Pasireotide treated patients with nausea (p=0,2675, 51,936%, 95% CI 40.401-63,32), hyperglycemia (p=0,0504, 43.268%, 95% CI 34.217-52.662) and diarrhea (p=0.3221,58,299%, 95% CI 46.658-69.299) must be applied.

Conclusions: The aggregated data on efficacy presented by meta-analysis could be used for the conduction of pharmacoeconomic analysis for the purposes of the assessment of orphan medicines efficiency.

Keywords: Orphan medicines in Bulgaria; rare diseases; meta-analysis; efficacy; safety.

ABBREVIATIONS

PDL: Positive Drug List; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; INNs: International Non-proprietary Names; RCTs: Randomized Clinical Trials; EU: European Union; ADRs: Adverse Drug Reactions; GAG: glycosaminoglycans; 6MWT: 6-minute walking test; UFG: Urinary Free Cortisol; ULN: upper limit of normal.

1. BACKGROUND

The advancement of medical science has improved the diagnostics of rare diseases and in the recent years the total number of all patients with rare diseases is around 6% of the world population [1]. Their medical needs should be satisfied despite the significantly high pharmacotherapy costs. Lots of incentives and possibilities for accelerated access to the market are available for all medicines with orphan designation. The scarcity of clinical evidence due to various reasons in the area of orphan medicines determines the necessity of further and additional reports presented by marketing authorization holders at least one year after fast tracking marketing authorization in order to prove the clinical benefits [2].

The limited number of eligible patients for clinical trials with orphan medicines, has led to the impossibility of proving the statistically significant differences between the existing and the new therapy [3]. The application of meta-analysis, which combines the results presented by studies with a similar design, could statistically demonstrate the significant clinical benefits of the new therapeutic option and ensures a precise evaluation of the medicines' efficacy [4].

To make a decision for orphan medicines listing and/or reimbursement the regulators need robust evidence for their efficacy and safety. Systematic reviews and meta-analyses could ensure such evidence.

The main goal of the current study is to evaluate the efficacy and safety of orphan medicines, included in the Bulgarian Positive Drug List (PDL) using the approaches of systematic reviews and meta-analysis.

2. MATERIALS AND METHODS

The study was performed in several steps. First, we analyzed the list of medicines with primary orphan designation, authorized for sale in the European Union by EMA. We searched Annex 1 of the Bulgarian PDL (16.12.2017) and found included reimbursed orphan medicines for ambulatory therapy.

The third step comprises of a systematic review of literature for the randomized clinical trials (RCTs) of efficacy and safety for the included 3 INNs. The systematic review was conducted in the following internet based scientific data basis: Pub Med, ClinicalTrials.gov, EU Clinical Trials Register. The key words used were efficacy,

safety and respective INN. A particular consistency was followed:

1. Defining of the study question: What is the existing evidence for the efficacy and safety of the orphan medicines?
2. Input of the key words in the data base PubMed Clinical Queries –INN of the drug, EFFICACY, SAFETY, name of the disease;
3. The studies were copied and analyzed. The duplicated studies were withdrawn from the analysis.
4. The technological scheme PRISMA Flow Diagram was applied.

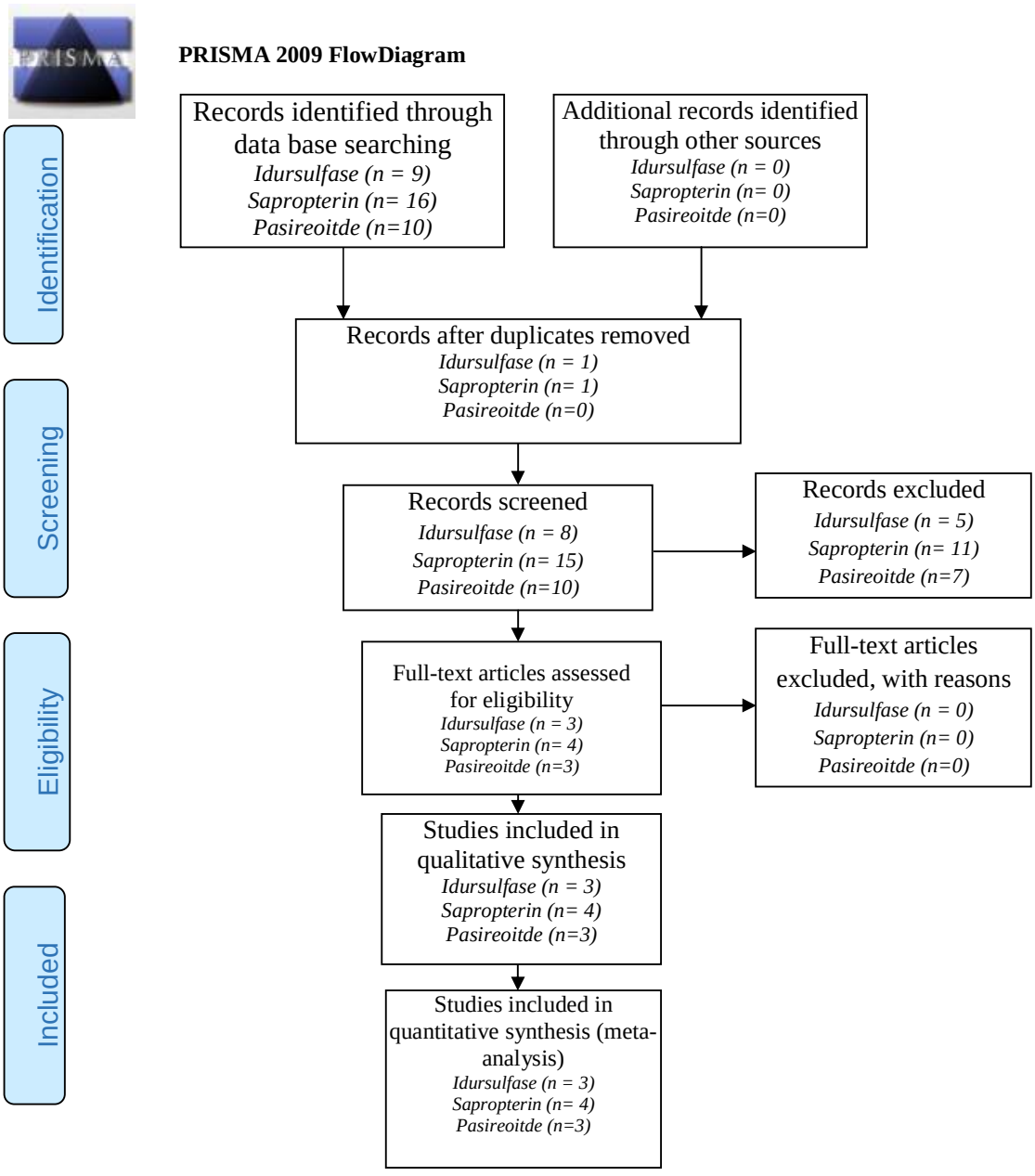

Fig. 1. Prisma flow diagram for the first 3 INN

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The studies were filtered on the basis of predefined inclusion and exclusion criteria. The inclusion criteria were as follows: All studies should be with a clinical focus; randomized or open-label studies with clearly presented outcome variables; Equal or similar time horizon; sufficient data about safety and efficacy processed with reliable statistical approaches. The determined exclusion criteria were a lack of response to the inclusion criteria.

During the last step, the eligible RCTs for every INN were processed with meta-analysis and comparison of proportions by statistical software MedCalc. The χ2-method for comparison of proportions. Steps in meta-analysis with MedCalc are: Statistics -> Meta-analysis -> Proportions. A heterogeneity test was performed and the conclusions were based on the level of significance of the results. Forest plot diagram was designed for each of the observed variables. The null hypothesis states that no statistical significant difference exists between the percentages [5].

3. RESULTS

The Positive Drug List in Bulgaria is consisted of 3 main annexes: Annex 1 includes fully or partly reimbursed medicines paid by the National Health Insurance Fund (NHIF); Annex 2: Medicines paid by the hospital budgets and annex 3: Medicines paid by the Ministry of Health budget. Orphan medicinal products and medicinal products intended to treat rare diseases are included in annex 1 and 2. Due to this reason we searched Annex 1 of the Bulgarian PDL and found reimbursed orphan medicines for ambulatory therapy.

There were 7 INNs of medicinal products intended to treat rare diseases with orphan designation, and with issued marketing authorization which was included in Annex 1 of PDL in Bulgaria - idursulfase, sapropterin dihydrochloride, pasireotide, tobramycin, ambrisentan, tafamidis, miglustat [6,7] (Table 1).

In this first part of the analysis are presented the results for three out of seven orphan medicines: Idursulfase, pasireotide and sapropterin. In Table 1 are presented their trade names, ATC codes and their mechanism of action specified in the Summary of Product Characteristics (SmPC) published in the web site of European Medicines Agency.

PRISMA Flow diagram presents the flow of information during different phases of the systematic review. It shows the number of the identified, included and excluded studies as well as the reasons for exclusion – Fig. 1. [8].

3.1 Results of the Systematic Review and Meta-analysis for Idursulfase

As shown on the PRISMA diagram 9 clinical studies about the efficacy and safety of Idursulfase were identified and only 3 out of them were included in the meta-analysis. The others were excluded due to different reasons such as: duplications, not relevant and significantly different design which does not match the others, the lack of clinical trial full text (Fig. 1).

The data about safety and efficacy results are presented in Tables 2 and 3. The patients' samples were combined on the basis of the patients' number with serious adverse drug reactions (ADRs). The efficacy was defined by the % of reduction in the levels of Glycosaminoglycan (GAG).

A meta-analysis of the efficacy data, measured with GAG reduction levels as a result of Idursulfase treatment is shown on Fig. 2. The heterogeneity test result is p= 0,0755 (>0.05), which rejects the null hypothesis for presence of significant difference between the results of different studies (Table 4 and Fig. 2). Therefore, a fixed effect result was taken into account. The total number of patients was 139, and the generalized percent reduction of GAG levels was 45,987% (95% CI from 37,6 to 54,546).

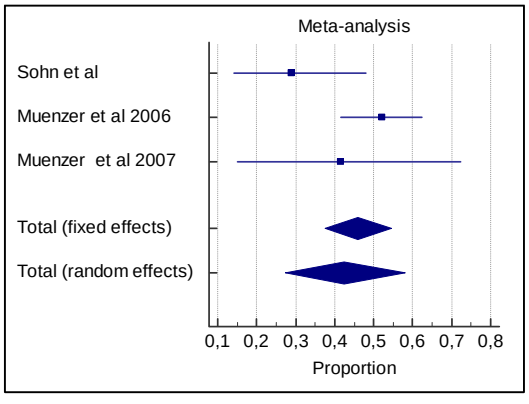

Fig. 2. Forest Plot diagram for GAG levels for Idursulfase

Table 1. Orphan medicinal products in Europe with European orphan designation and European marketing authorization, included in the Bulgarian PDL

Trade name	INN	ATC code	Rare disease	ICD code	Mechanism of action
Elaprase	idursulfase	A16AB09	Hunter disease	E76.1	Catabolize the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate by cleavage of oligosaccharide -linked sulfate moieties
KUVAN	sapropterin dihydrochloride	A16AX07	hyperphenylalaninaeia; PKU	E70.0	Enhance the activity of the defective phenylalanine hydroxylase
SIGNIFOR	pasireotide	H01CB05	Cushing's disease	E24.0	Leads to inhibition of ACTH secretion
TOBI PODHALER	tobramycin	J01GB01	Cystic Fibrosis	E84.0	Aminoglycoside antibiotic which disrupt protein synthesis
VOLIBRIS	ambrisentan	C02KX02	Pulmonary arterial hypertension	I27.0,M34.0, M34.1,M34.2	ERA selective for the endothelin A (ET_A) receptor
VYNDAQEL	tafamidis	N07XX08	transthyretin amyloidosis	E85.1	A specific stabilizer of transthyretin
ZAVESCA	miglustat	A16AX06	Niemann-Pick type C disease.	E75.2	A competitive and reversible inhibitor of the enzyme glucosylceramide synthase

Table 2. Data extracted from the analyzed studies

Study	Total_patients	GAG	Number of patients with serious ADR	Patients with urticaria
Sohn et al	31	9	3	3
Muenzer et al 2006	96	50	24	5
Muenzer et al 2007	12	5		

***GAGR -** GAG levels reduction, **6MWT –** 6-minute walking test*

Table 3. Clinical trials for Idursulfase

No	Authors	Design	Number of patients	Efficacy results	Adverse drug reactions	Conclusion
1	Sohn et al. [9]	Randomized, single-blinded, active comparator-controlled phase I/II trial for 24 weeks.	31 MPS II patients between 6 and 35 years of age	• % changes of urine GAG levels were greater in 0.5 and 1.0 mg/kg/week idursulfase beta groups than in the comparator group (-29.5±15.5 vs. -18.7±15.8, P = 0.043 and -41.1±10.2 vs. -18.7±15.8, P = 0.002, respectively). • % change in the 6MWT distance was significantly increased in the idursulfase beta 0.5 mg/kg/week group (23.52±16.90 vs. -2.66±9.19, P = 0.003) and the idursulfase beta 1.0 mg/kg/week group (12.71±11.91 vs.	• 4 cases in 1/10 subjects (10%) in the idursulfase beta 0.5 mg/kg group, three cases occurred in 2/10 subjects (20%) in the idursulfase beta 1.0 mg/kg group, and 19 cases occurred in 2/11 subjects (18.6%) in the comparator group.	Idursulfase beta generates clinically significant ***reduction of urinary GAG***, ***improvements in endurance*** as measured by 6MWT, and it has an ***acceptable safety profile*** for the treatment of MPS II.

No	Authors	Design	Number of patients	Efficacy results	Adverse drug reactions	Conclusion
				-2.66±9.19, P = 0.015) compared to the comparator group.	• Urticaria (19 cases) was reported most frequently, followed by rash (4 cases), itching (2 cases), and wheezing (1 case).	
2	Muenzer et al. [10]	Randomized, double-blind, placebo-controlled trial for 24 weeksfollowed by an open-label extension study.	• 3 groups of 4 patients • The first group received idursulfase at 0.15 mg/kg every other week; • The 2nd and 3rd groups: 0.5 and 1.5 mg/kg, respectively.	• Urinary glycosaminoglycans were reduced within 2 weeks of initiating idursulfase and were decreased 49% after 48 weeks of treatment (P<0.0001); • The 6-minute walk test distance (6MWT) increased an average of 48 meters after 48 weeks (P=0.013).		Idursulfase was well tolerated and was associated with ***reductions in urine glycosaminoglycans levels*** and organ size, as well as ***an increased 6-minute walk test distance.***
3	Muenzer et al. [11]	Double-blind, placebo-controlled trial, 53 weeks	96 patients between 5 and 31 years of age • 3 groups: placebo infusions; weekly idursulfase (0.5 mg/kg) infusions; every-other-week infusions of idursulfase (0.5 mg/kg).	• The weekly dosing group experienced a 37-m increase in the 6-minute-walk distance (P = 0.013); • 2.7% increase in percentage of predicted forced vital capacity (P = 0.065); • 160 mL increase in absolute forced vital capacity (P = 0.001) compared to placebo group at 53 weeks; • 6MWT distance was significantly increased compared to placebo (44.3 ± 12.3 m versus 7.3 ± 9.5 m, P = 0.0131); • Spleen volume remained reduced in the idursulfase groups compared to placebo (−25.1 ± 2.4% in the idursulfase weekly group, −19.8 ± 3.2% in the idursulfase EOW group, and +7.2 ± 4.2% in the placebo group, *P*< 0.0001 for placebo compared to either idursulfase group); • 26 of 64 (40.6%) had normalized urine GAG levels, and the majority of the remainder of idursulfase-treated patients were approaching the upper end of the normal range (≤127 µg GAG/mg creatinine); • Idursulfase antibodies were detected in 46.9% of patients during the study.	• The total number of AEs was similar in each group (placebo, 992; Weekly, 1,063; EOW, 1,163); • 49 serious adverse events (SAEs) occurred in 26 patients	This study ***supports the use of weekly infusions*** of idursulfase in the treatment of mucopolysaccharidosis II.

Table 4. Heterogeneity test for GAG data

Q	5,1680
DF	2
Significance level	P = 0,0755
I^2 (inconsistency)	61,30%
95% CI for I^2	0,00 to 88,97

A meta-analysis for the safety of Idursulfase regarding the ADRs urticaria and serious ADRs is shown on Fig. 3. Fixed effect was determined in patients who experienced urticaria (P = 0,3459, 6,81%, 95% CI from 3,126 to 12,623) (Fig. 3 and Table 5) and serious ADRs (P = 0,0619, 21,27%, 95% CI from14,561 to 29,345) (Fig. 4 and Table 6), which proves the lack of statistically significant differences regarding the number of patients with urticaria and serious ADRs.

Table 5. Heterogeneity test for urticaria

Q	0,8886
DF	1
Significance level	P = 0,3459
I^2 (inconsistency)	0,00%
95% CI for I^2	0,00 to 0,00

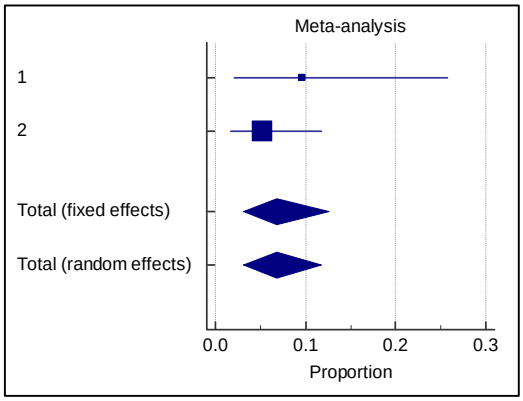

Fig. 3. Forest Plot diagram forurticarial for Idursulfase

Table 6. Heterogeneity test for serious ADRs

Q	3,4846
DF	1
Significance level	P = 0,0619
I^2 (inconsistency)	71,30%
95% CI for I^2	0,00 to 93,55

Comparison of proportion did not show any statistically significant difference among the share of patients with urticaria and serious ADRs (p = 0,3718 and p = 0,0775, respectively).

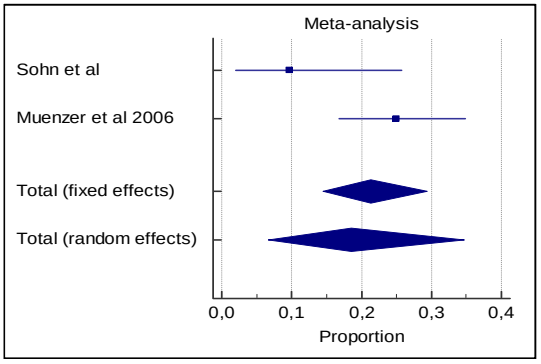

Fig. 4. Forest Plot diagram for serious ADRs for Idursulfase

3.2 Results from the Systematic Review and Meta-analysis for Sapropterin

The PRISMA flow diagram for the clinical trials with Sapropterin shows the number of excluded studies (n=11). The reasons for exclusion of the studies were associated with differences in the time horizon of the studies, in the design of the studies, a lack of full text and duplication (Fig. 1).

The analyzed data were for the number of patients with adverse drug reactions after the application of Sapropterine. Meta-analysis about the efficacy was not performed for the lack of relevant and similar studies which could be combined through meta-analysis methods.

The input data for meta-analysis are presented in Table 7. The number of patients with adverse drug reaction reported in the studies of Scala, 2015 and Bushueva, 2014 were 7 and 24, respectively. The same number of patients from the other studies of Burton, 2011 and Lee, 2008 were 93 and 68 (Table 8).

Table 7. Data extracted from the analyzed studies for Sapropterin

Study	Total patients	Number of patients with AEs
Scala et al. 2015	17	7
Bushueva et al	90	24
Burton et al	111	93
Lee et al	80	68

Table 8. Clinical trials for Sapropterin

No	Authors	Design	Number of patients	Efficacy results	Adverse drug reactions results	Conclusion
1	Scala et al. [12]	open-label interventional trial with long-term oral BH4 therapy	17 PKU patients	• The reduction of blood Phe from the baseline among BH4 responders ranged between 33.3% and 77.1%. • Mean tolerance was 583 ± 443 mg Phe/day before BH4 therapy and 2798 ± 1568 mg Phe/day during BH4 treatment ($p < 0.0001$)	Adverse events were recorded in 7 patients (41%)	BH4 is safe and effective in increasing tolerance to Phe while keeping a good metabolic control.
2	Bushueva et al.[13]	open, non-comparative clinical study	90 patients with PKU	• Positive response to treatment in 30 (33.3%) patients (95% CI 23.7-44.1); • The mean percentage change in Phe blood levels after the 8-day response test period compared to Phe levels prior to dosing was 14.1 ± 28.4% in the overall subject population (95% CI 8.2-20.1) and 44.3 ± 15.1% in the subpopulation of patients with a positive response (95% CI 38.6-49.9).	Adverse events were reported in 24 (26.7%) patients in the overall population in 16 (53.3%) patients in the subpopulation who had a response.	Confirmed efficacy and safety of sapropterin therapy in patients with PKU,
3	Burton et al. [14]	Phase 3b, multicenter, multinational, open-label, 3-year extension trial	111 subjects aged 4-50 years		AEs were reported for 93 (83.8%) of the 111 subjects; Drug-related AEs were reported for 37 (33.3%) of 111 subjects; The most common drug-related AEs were viral gastroenteritis, vomiting, and headache (each 4.5% of subjects).	Sapropterin treatment was found to be safe and well tolerated at doses of 5 to 20mg/kg/day for an average exposure of 659 days
4	Lee et al[15]	multicenter, open-label extension study	80 > or =8 years old	• The average plasma phenylalanine concentration was reduced from 14.7 at baseline to 10.7mg/dl in week 10, then maintained through week 22	Sixty-eight (85%) patients had at least one adverse event (AE).	Sapropterin is effective in reducing plasma Phe concentrations in a dose-dependent manner and is well tolerated at doses of 5-20 mg/kg/day over 22 weeks in BH4-responsive patients with PKU.

A fixed effect result was taken into account in patients who experienced ADRs (P = 0,2264, 29,237%, 95% CI from 20,916 to 38,720) (Fig. 5 and Table 9), which proves the lack of statistically significant differences regarding the number of patients with urticaria and serious ADRs. The same fixed effect was used for the other two studies (Burton, 2011 and Lee, 2008) – the total number of patients in both studies were 191 and 83,945% of them were with ADRs (95% CI from 77,99 to 88,824) (Table 10 and Fig. 6).

Table 9. Heterogeneity test for ADRs

Q	1,4633
DF	1
Significance level	P = 0,2264
I^2 (inconsistency)	31,66%
95% CI for I^2	0,00 to 0,00

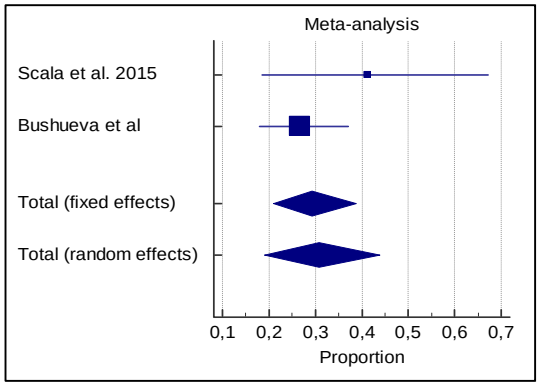

Fig. 5. Forest plotdiagram for ADRs for sapropterin

Table 10. Heterogeneity test for ADRs

Q	0,04150
DF	1
Significance level	P = 0,8386
I^2 (inconsistency)	0,00%
95% CI for I^2	0,00 to 0,00

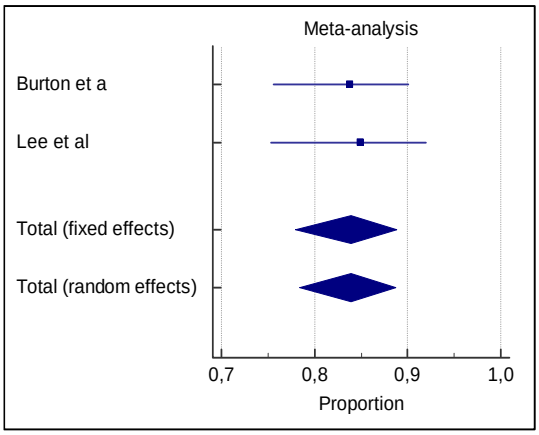

Fig. 6. Forest Plotdiagram for ADRs for Sapropterin

The comparison of proportion confirms a lack of statistically significant difference among the percent of patients with ADRs for all studies (p=0,8225 (>0,05) and p=0,2354 (>0,05), respectively).

3.3 Results of the Systematic Review and Meta-analysis for Pasireotide

Only 3 clinical trials for Pasireotide were included due to several reasons: one of the identified studies was a literature review without any data from conducted clinical trials; another did not present enough relevant information; the design of most of the studies was not similar and only one study was about the quality of life (Fig. 1).

Several clinical studies demonstrated that the levels of urinary free cortisol could be controlled after Pasireotide treatment of patients with Cushing syndrome. A safety profile regarding the rate of some of most common ADRs such as diarrhea, nausea and hyperglycemia was tested through meta-analysis (Tables 11 and 12).

Table 11. Data extracted from the analyzed studies for Pasireotide

Study	Total number of patients	Patients with controlled UFC (UFC ≤ ULN) at month 24	Patients with diarrhea	Patients with nausea	Patients with hyperglycemia
1	58	20	32	28	23
2	19	4	13	12	13
3	39	15			14

Table 12. Clinical trials for Pasireotide

No	Authors	Design	Number of patients	Efficacy results	Adverse drug reactions	Conclusion
1	Schopohl et al. [16]	open-ended, open-label extension to a randomized, double-blind, 12-month, Phase III study.	58 patients with mean UFC ≤ ULN at month 12 from the core study Dose: 300-1,200 μg bid	• 0.0% (29/58) and 34.5% (20/58) had controlled UFC (UFC ≤ ULN) at months 12 and 24, respectively; • The mean percentage decrease in UFC was 57.3% (95% CI 40.7-73.9; n = 52) and 62.1% (50.8-73.5; n = 33) after 12 and 24 months' treatment, respectively.	diarrhea (55.6%), nausea (48.1%), hyperglycemia (38.9%), and cholelithiasis (31.5%) SAEs caused by Pasireotide 600 23/82 (28.05%) and by Pasireotide 900 (25/80 (31.25%)	***Improvements in the clinical signs*** of Cushing's disease.
2	Trementino et al.[17]	phase III trial	a case of a 55-year-old woman with CD and DM	• 1,200 μg bid) normalized UFC levels and restored cortisol rhythm; • Five years later, the patient is still receiving pasireotide (300 μg bid) with no loss of clinical or biochemical efficacy and with continued glycemic control.		To support the long-term continuation of pasireotide.
3	Boscaro et al.[18]	open-ended, single-arm, multicenter extension study (primary endpoint: 6 months). median treatment duration in the extension was 9.7 months	18 years with Cushing's disease who completed the core study Of the 38 patients who completed the core study,19 entered the extension and 18 were included in the efficacy analyses	56% of the 18 patients had lower UFC than at core baseline and 22% had normalized UFC	The most common adverse events were mild-to-moderate gastrointestinal disorders and hyperglycemia. During the treatment period, hyperglycemia-related AEs were reported in 68 % of patients (13/19). Diarrhea - 13 (68.4%) Nausea - 12 (63.2) Hyperglycemia - 11 (57.9) Abdominal pain - 9 (47.4) Headache - 7 (36.8) Injection-site pain - 6 (31.6) Dizziness - 5 (26.3) Fatigue - 5 (26.3) Injection-site pruritus – 5 (26.3)	Pasireotide offers a tumor-directed medical therapy that may be effective for the extended treatment of some patients with Cushing's disease.

**UFC - Urinary Free Cortisol*ULN - upper limit of normal*

Table 13. Heterogeneity test for efficacy data

Q	24,1976
DF	2
Significance level	**P < 0,0001**
I^2 (inconsistency)	91,73%
95% CI for I^2	78,94 to 96,76

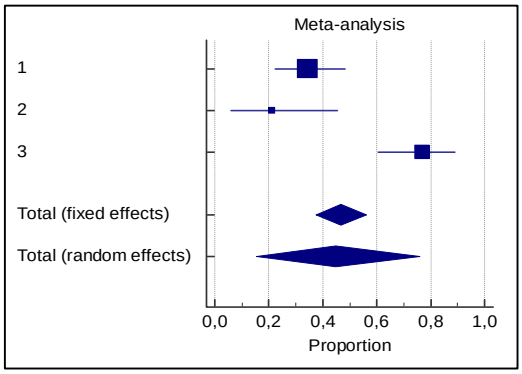

Fig. 7. Forest Plotdiagram for efficacy data of Pasireotide

The result of the heterogeneity test showed that p<0,0001 (<0,05), which rejected the null hypothesis for lack of statistically significant difference between the analyzed percentages. Therefore, the random effect result must be considered for estimation of the generalized result. The total number of patients is 116 and the percent of patients with controlled levels of UFC is 44,81%, (95% CI from 37,506 to 56,073) (Table 13 and Fig. 7).

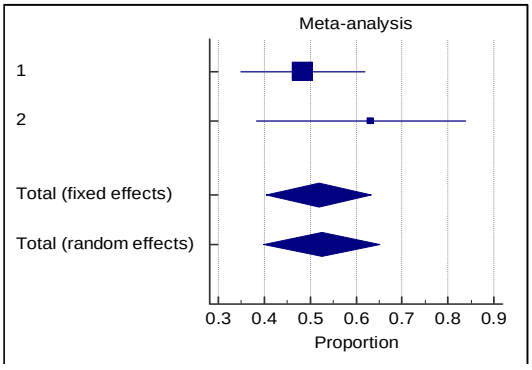

Fig. 8. Forest Plot diagram for nausea for Pasireotide

After the application of Chi-squared test for the comparison of two proportions (from independent samples), expressed as a percentage, p value was less than 0.05 which means that the proportions differ significantly (p=0.0001).

A meta-analysis for the safety of Pasireotide regarding the ADRs – diarrhea, nausea, and hyperglyceamia was performed. Fixed effect was used for all ADRs: Nausea (p=0,2675, 51,936%, 95% CI from 40.401 to 63,32) (Fig. 8), hyperglycemia (p=0,0504, 43.268%, 95% CI 34.217-52.662) (Fig. 9) and diarrhea (p=0.3221, 58,299%, 95% CI 46.658-69.299) (Fig. 10). There are no statistically significant differences regarding the number of patients with diarrhea, nausea and hyperglycemia in the observed samples.

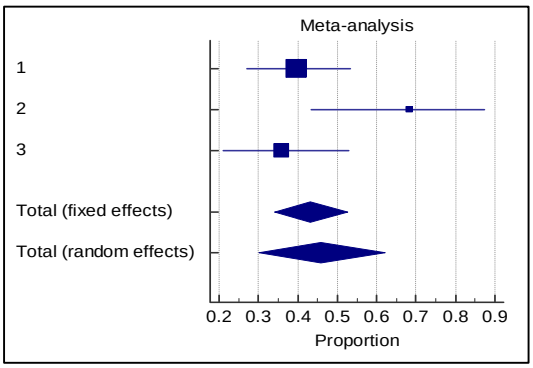

Fig. 9. Forest Plot diagram for hyperglycemia for Pasireotide

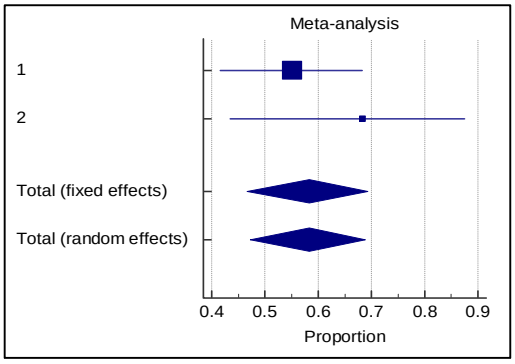

Fig. 10. Forest Plot diagram for diarrhea for Pasireotide

4. DISCUSSION

To the best of our knowledge this is the second meta-analysis performed in Bulgaria about the efficacy and safety of orphan medicines. The previous one was about the efficacy and safety of Bosutinib, published by the same authors, which explains the similarity of the used methods. The performed meta-analysis demonstrates the efficacy and safety of Idursulfase and Pasireotide as well as the safety of Sapropterine. The results of current study

could be used as a primary point for improving the process of conducting pharmacoeconomic evaluations for the purposes of pricing and reimbursement decisions about orphan medicinal products in Bulgaria.

The aggregated data during the meta-analysis shows that the reduction of GAG levels as a consequence of the treatment with Idursulfase is defined to be approximately 46%, which could be considered as the likely effectiveness of the INN. The ADR urticarial is expected to occur in approximately 7% of the patients and serious ADRs in 21% of the treated patients. An Enzyme replacement therapy with Idursulfase is effective and safe, but additional studies are necessary to be conducted in order to confirm the results. Only one meta-analysis which combined 5 clinical trials in 2012 confirms a statistically significant increase of the values for forced vital capacity (FVC) and for 6-minute walk test distance**.** (6MWT).Those clinical outcomes were not considered in our study. The authors concluded that the therapy with Idursulfase is safe and brings potential benefits for patients with e MPS II [19].

Approximately 86% of the patients to whom Sapropterin was prescribed reported adverse drug reactions as a result of the performed meta-analysis of safety studies. The expected effectiveness regarding the reduction of Ph levels reported by all studies is statistically significant. Our study could not demonstrate the expected effectiveness due to lack of similarity among the studies. A published systematic review from 2013 concluded that Sapropterin leads to improvement in short-term outcomes such as phenylalanine levels reduction, but no evidence about long-term clinically important outcomes such as cognition, executive function, and quality of life exist [20]. Somaraju et al. published a systematic review about the safety and efficacy of Sapropterin and confirmed the availability of short-term benefits from using Sapropterin, lack of evidence on the long-term effects and demonstrated a lack of serious adverse events in a short-term period of time [21]. A hierarchical meta-analysis by Fonnesbeck et al. [22] was performed, but it was oriented to other goals. It was focused on the calculation of blood Phe-IQ correlation in order to predict what the possibility of low IQ for a particular range of phenylalanine level is [22]. Therefore, a meta-analysis could be performed after the collection of enough evidence for the long-term effectiveness of Sapropterin.

The combined random effect for the effectiveness of Pasireotide demonstrated significant high number of patients with adequate control regarding the urinary free cortisol levels (approximately 44.81%). Any published meta-analysis about the efficacy and safety of Pasireotide among patients with Cushing syndrome was found in the scientific literature. Only a systematic review and meta-analysis of somatostatin analogues (Pasireotide and others) in the prevention of postoperative complications after pancreaticoduodenectomy was published [23]. A systematic literature review reaffirms that Pasireotide is appropriate treatment for patients with Cushing disease for whom surgery is not possible or for whom surgery has failed and demonstrated the clinical benefits of the therapy without applying a meta-analysis [24].

Several limitations of the current study could be outlined such as disadvantages in performing a literature search and the lack of more complex and reliable methods for disaggregation and analyzing the results of the clinical studies. Moreover, using more specific software for the performance of meta-analysis should be considered. These limitations could be overcome by applying more comprehensive methods for analyzing the published clinical studies.

Despite the limitations, the aggregated data on efficacy presented by the meta-analysis could be used for the conduction of cost-effectiveness analysis for the purposes of cost-effectiveness assessment of the orphan medicines, evaluated in the current study. Therefore, a more reliable and precise assessment using meta-analysis could be done for the purposes of decision making for inclusion and exclusion of orphan medicines from the PDL.

5. CONCLUSION

This study shows that Idursulfase, Pasireotide and Sapropterin are with proven efficacy and safety. Therefore, the patients' access to these medicines is crucial for the purposes of controlling their rare condition. We can also conclude that the performance of meta-analysis for orphan medicines meets various difficulties and challenges such as lack of similar and reliable clinical trials which can be combined. The importance of such an analysis is undeniable, yet lots of gaps in the realization of this type of analysis for orphan medicines still exist.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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