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ORIGINAL ARTICLE

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Repurposing empagliflozin in individuals with glycogen storage disease Ib: A value-based healthcare approach and systematic benefit-risk assessment

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Abstract

Off-label repurposing of empagliflozin allows pathomechanism-based treatment of neutropenia/neutrophil-dysfunction in glycogen storage disease type Ib (GSDIb). From a value-based healthcare (VBHC) perspective, we here retrospectively studied patient-reported, clinical and pharmacoeconomic outcomes in 11 GSDIb individuals before and under empagliflozin at two centers (the Netherlands [NL], Austria [AT]), including a budget impact analysis, sensitivity-analysis, and systematic benefit–risk assessment. Under empagliflozin, all GSDIb individuals reported improved quality-of-life-scores. Neutrophil dysfunction related symptoms allowed either granulocyte colony-stimulating factor cessation or tapering. Calculated cost savings per patient per year ranged between € 6482–14 190 (NL) and € 1281–41 231 (AT). The budget impact analysis estimated annual total cost savings ranging between € 75 062–225 716 (NL) and € 37 697–231 790 (AT), based on conservative assumptions. The

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systematic benefit-risk assessment was favorable. From a VBHC perspective, empagliflozin treatment in GSDIb improved personal and clinical outcomes while saving costs, thereby creating value at multiple pillars. We emphasize the importance to reimburse empagliflozin for GSDIb individuals, further supported by the favorable systematic benefit-risk assessment. These observations in similar directions in two countries/health care systems strongly suggest that our findings can be extrapolated to other geographical areas and health care systems.

KEYWORDS

drug repurposing, glycogen storage disease type Ib, inborn metabolic diseases, off-label treatment, rare diseases, value-based health care

1 | INTRODUCTION

Glycogen storage disease type Ib (GSDIb; MIM #232220) is an ultra-rare inherited disorder of carbohydrate metabolism caused by pathogenic biallelic variants in the *SLC37A4* gene, underlying glucose-6-phosphate transporter (G6PT) deficiency.[1] The clinical phenotype is characterized by fasting intolerance, hepato(spleno)megaly, short stature, and neutropenia and neutrophil dysfunction related symptoms such as bacterial infections, mucocutaneous lesions, and inflammatory bowel disease (IBD). For at least three decades, these life-threatening GSDIb symptoms were treated with recombinant human granulocyte colony-stimulating factor (G-CSF).[2] G-CSF increased neutrophil counts and markedly improved the prognosis for people with GSDIb. However, G-CSF failed to (fully) restore neutrophil functions, and long-term G-CSF use in GSDIb can lead to serious adverse effects (such as splenomegaly and hematological malignancies). Furthermore, G-CSF requires painful subcutaneous injections several times per week or even daily and is expensive.[3]

1,5-anhydroglucitol-6-phosphate (1,5-AG6P) is a structural analog of glucose-6-phosphate. Deficiency of G6PT results in failure to eliminate 1,5-AG6P and its accumulation within the neutrophils leads to energy deficits and subsequent apoptosis.[4] This explains the neutrophil dysfunction and neutropenia in GSD Ib and implicates a treatment option. Sodium glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, are anti-diabetic drugs that inhibit renal glucose reabsorption, thus causing glucosuria. Glucosuria decreases renal 1,5AG reabsorption and thereby lowering its serum concentration and improving neutrophil dysfunction and neutropenia.[5] It was subsequently demonstrated that the off-label use of empagliflozin allowed successful treatment of neutropenia and neutrophil dysfunction-related symptoms in 112 GSDIb individuals; most importantly G-CSF dosing was discontinued in 55% and reduced in another 17% of the cases.[6] Additional analysis of patient-reported outcome measures (PROM) showed improvement in several domains, such as appetite, level of activity, overall well-being, and sleep.[7] Nevertheless, in many geographic areas and health care systems empagliflozin is not reimbursed for people with GSDIb, limiting access to this new treatment option.

Value-based healthcare (VBHC) initially was defined as health outcomes achieved per monetary unit spent for the full-cycle of care for an individual's medical condition.[8] A more comprehensive concept of VBHC has identified four value-pillars: appropriate care to achieve individuals' personal goals (personal value), achievement of best possible outcomes with available resources (technical value), equitable resource distribution across all groups of affected individuals (allocative value), and contribution of healthcare to social participation and connectedness (societal value).[9] VBHC is generally applied to high volume, low complexity medical conditions, but this approach is challenging in rare diseases.[10] Here we investigate repurposing the off-label empagliflozin treatment of persons with GSDIb, showcasing a meaningful application of VBHC principles to an ultra-rare disease.[11] We demonstrate for the first time that empagliflozin treatment in GSDIb improved personal and clinical outcomes while saving costs at the same time.

2 | MATERIALS AND METHODS

2.1 | Study design, study population, and statistical analysis

This is a retrospective, multicenter, non-interventional study on PROMs, clinical, and pharmacoeconomic

outcomes. Data of all GSDIb individuals using empagliflozin, treated at the University Medical Center Groningen (UMCG), the Netherlands (NL) and University Children's Hospital Salzburg (UCHS), Austria (AT) were retrieved from the electronic medical files and stored in a local database. Additionally, affected individuals or parents completed either an interview or a questionnaire.

2.2 | Ethical considerations

All individuals were treated on an individual base and data used were collected during regular clinical care and one additional telephone/video consultation with affected individuals/parents. Informed oral and written consent for the off-label treatment with empagliflozin was obtained from the patients or parents. No specific ethics vote was necessary for this study.

2.3 | Data sources

2.3.1 | Patient-reported outcomes

PROMs, including the locally used Groningen reported outcome measures (GROMs), were collected during regular clinical visits or video/telephone consultation using a questionnaire (Supplementary file 1). All affected individuals (respectively the parents of young children) were asked to rate their quality of life (QoL; scale from 0 to 10, 10 being the best) before the start of empagliflozin and under empagliflozin, retrospectively.

2.3.2 | Clinical outcomes

The following data were retrieved from the medical records: dosage of G-CSF and empagliflozin, laboratory values, (pediatric) Crohn Disease Activity Index ((P)CDAI) scores[12,13] at last visit before start of empagliflozine and after 1 year of follow up (UMCG) or at most recent visit (UCHS). Additionally, the number of medical consultations/contacts (general practitioner visits (only UCHS), outpatient clinic visits (only UCHS), emergency room visits, hospitalizations, and ambulance rides) were collected from 1 year before the start of empagliflozin until 1 year of follow up (UMCG) and for the same time before and after start of empaglfozin (UCHS). The data from the medical records were additionally verified with the affected individuals/parents during a retrospective interview.

2.3.3 | Pharmacoeconomic outcomes

The cost prices were used based on national norms (NL)[14] or estimated by expert advisors (AT) and are listed in Supplementary file 2, providing insight into the price per person per day for G-CSF and empagliflozin, respectively. For NL, calculations compared the year before empagliflozin treatment with the first year under treatment. For AT, calculations compared the time under empagliflozin versus the same time period before the start of empagliflozin, calculated as mean annual costs.

A **budget impact analysis** extrapolated the total savings for medication costs for one and 3 years in both countries. In NL 18 individuals with GSDIb (Dutch Diagnosis Registration Metabolic Diseases [DDRMD, https://ddrmd.nl/]) and in AT 12 individuals (national registry for inborn metabolic diseases)[15] were registered at the time this study was conducted. The budget impact analysis was performed for two extreme scenarios, to reflect variations in the percentage of GSDIb individuals on G-CSF in both countries as much as possible. In **scenario 1,** we conservatively assumed that 32% of all GSDIb individuals used G-CSF based on Visser et al.[16] **Scenario 2** was calculated based on our own clinical expertise, according to which most persons with GSDIb were on G-CSF before treatment with empagliflozin was known (17 out of 18, and 12 out of 12, at UMCG and UCHS, respectively). For both scenarios we assumed that at least 55% of the affected individuals could discontinue G-CSF under empagliflozin (based on Dale et al.).[2] Due to the low birth prevalence of GSDIb (estimated 1/1000000 births), and national birth rates per year (approximately 175 000 (NL)[17] and 85 600 (AT)[18]) it can be predicted that no GSDIb individual may be born in the next 3 years. Therefore, we calculated the budget impact for 1 and 3 years periods.

A **sensitivity analysis** extrapolated the impact of G-CSF doses and G-CSF vial discarding on the total annual medication costs before and under empagliflozin for a single, hypothetical person with GSDIb in both countries, based on literature based scenarios.[2,5,6] We performed the calculations for a 33 kg person (based on the average age of all published individuals with GSD1b treated with empagliflozin of 12.8 years[6] and the corresponding p50 weight for p50 height on the Dutch growth charts) only using the required G-CSF not discarding the vial.

2.4 | BRAvO assessment

To analyze the benefits and risks of off-label empagliflozin use in GSDIb, the structured Benefit and Risk

Assessment for Off-label use (BRAvO) decision framework was followed.[19]

3 | RESULTS

3.1 | Participants and medication

The general characteristics of 11 persons with GSDIb, their PROMs, clinical, and pharmacoeconomic outcomes before and during empagliflozin are summarized in Table 1 (UMCG) and Table 2 (UCHS).

Seven out of 11 participants were able to stop G-CSF under empagliflozin treatment, and G-CSF doses were reduced in the remaining four participants. Of note, some spillage of G-CSF occurred since once opened, G-CSF vials cannot be stored and reused. This effect was accounted for when cost savings were calculated.

3.2 | PROMs

For eight out of 11 persons with GSDIb Qol data were available; median QoL score improved from 3.0 to 8.5. Supplementary file 3 lists a selection of quotes from GSDIb individuals and caregivers obtained during the interviews.

3.3 | Clinical outcomes

Neutrophil counts increased in 8/11 and were within normal range in 6/11 participants during empagliflozin. (P) CDAI improved in seven participants after empagliflozin, and normalized in two. All participants demonstrated significant improvement concerning neutrophil dysfunction related findings (e.g., mucocutaneous lesions, infections, and inflammatory bowel disease).

3.4 | Pharmacoeconomic outcomes

Four out of seven GSDIb individuals treated at UMCG were living outside NL. Because of differences between organization and costs of health care between NL and their countries of residence, these costs were deemed not suitable and excluded in this part of the analysis.

In both countries, medication costs accounted for the largest share. During the interviews it became clear that participants I, III, and IV applied temporary G-CSF dosage adjustments based on their symptoms. These adjustments were incorporated in the pharmacoeconomic calculations. Cost savings per patient per year ranged between € 6482–14 190 (NL) and € 1281–41 231 (AT).

Table 3 shows the detailed **budget impact analysis** for 25 mg/day empagliflozin in persons with GSDIb in two nationwide scenarios. The literature based scenarios would lead to a range of annual total cost savings of € 75 062–225 716 (NL) and € 37 697–231 790 (AT), whereas calculated cost savings per patient per year ranged between € 25 021–25 080 (NL) and € 18 849–19 316 (AT).

After addressing the end-users (i.e., the GSDIb individuals and their families) and the prescribers, we modeled the impact of the producer and the supplier in the **sensitivity analysis** (Table 4). Approximately 98% cost reduction would be achieved in both countries when comparing scenario 1 (all individuals solely use G-CSF) and 6 (all individuals discontinue G-CSF and solely use empagliflozin).

The structured **BRAvO** was found to be in favor of empagliflozin treatment and is included as Supplementary file 4.

4 | DISCUSSION

This is the first study addressing the repurposing and off-label treatment with empagliflozin in individuals with GSDIb from a VBHC perspective. This is a challenging approach, because VBHC principles are mainly applied in medical conditions with high prevalence and low complexity. In rare diseases, outcomes are frequently uncertain, jeopardizing the use of value based models. However, we show in this study, that even for an ultra-rare condition such as GSDIb VBHC principles can be reliably applied, potentially supporting reimbursement decisions.

Our findings show that empagliflozin treatment reduces costs and improves quality of life in GSDIb and thereby increases **allocative value** (i.e., cost-savings and distribution of resources according to needs). As there is a large heterogeneity in persons with GSDIb, we did not only show the cost-savings for our own Dutch and Austrian cohorts (Tables 1 and 2) but also for several literature-based scenarios in both the budget impact analysis and the sensitivity analysis (Tables 3 and 4) to model variances in costs due to different treatment regimens. We identified the frequency of G-CSF injections as major determinant of costs. Interestingly, there is a discrepancy in cost reduction between the countries (34% [NL] and 96% [AT]) which is attributable to the fact that some Dutch individuals still used G-CSF while it was stopped in all Austrian individuals. Nevertheless, our observations point toward similar directions in both countries suggesting that our findings are likely to be relevant for other countries as well.

TABLE 1 General characteristics, patient-reported outcomes, clinical, and pharmacoeconomic outcomes before/under empagliflozin (UMCG).

General characteristics	Participant I (PT3 in Wortmann et al.[5])		Participant II		Participant III		Participant IV		Participant V		Participant VI	
Country of residence	The Netherlands		Italy		The Netherlands		The Netherlands		South-Africa		Germany	
Sex	M		F		M		F		M		M	
Date of start empagliflozin treatment (dd-mm-yyyy)	27-06-2019		11-09-2019		12-10-2019		26-03-2021		01-06-2021		10-08-2021	
Age at start empagliflozin treatment (y,m)	6y10m		1y11m		11y2m		13y0m		8 m		19y8 m	
SLC37A4 variants												
Nucleotide change (NM_001164277.2)	c.1042_1043del		c.1042_1043del		c.365G > A		c.1042_1043del		c.287G > A		c.242_246del	
	c.1042_1043del		c.899G > A		c.365G > A		c.1042_1043del		c.287G > A		c.381 + 2G > T	
Predicted protein change (NP_001157749.1)	p.(L348Vfs*53)		p.(L348Vfs*53)		p.(G122E)		p.(L348Vfs*53)		p.(W96*)		p.(S81Wfs*28)	
	p.(L348Vfs*53)		p.(R300H)		p.(G122E)		p.(L348Vfs*53)		p.(W96*)		splicing	
Patient reported outcomes	**BE**	**UE**	**BE**	**UE**	**BE**	**UE**	**BE**	**UE**	**BE**	**UE**	**BE**	**UE**
QoL Score (Scale 0–10)	2	10	2	7	5	10	6	8	3	8	7	9
Clinical outcomes												
G-CSF (ug/kg/d)	7.0	0.6	1.3	0.6	6.8	1.5	3.2	0.5	28	0	3.3	0
Empagliflozin (mg/kg/d)	0	0.6	0	0.6	0	0.7	0	0.4	0	0.4	0	0.3
Neutrophil count (10^9/L)	1.2	2.6	1.9	2.9	2.7	0.3	0.3	0.4	0.4	0.8	0.9	1.0
Hemoglobin (mmol/L)	6.1	7.1	8.1	8.3	6.2	6.7	6.3	8.0	6.8	7.3	8.6	9.4
PCDAI	32.5	17.5	20	7.5	40	20	15	17.5	30	0	24	12
Hospital (ICU) admissions /y	7	3	2	1	0	0	0	0	0	0	0	0
Emergency room visits/y	7	2	4	0	0	0	0	0	i.n.a.	i.n.a.	0	0
Ambulance rides/y	2	0	0	0	0	0	0	0	i.n.a.	i.n.a.	0	0
Pharmacoeconomic outcomes												
G-CSF costs (€/y)	24 134	24 134			12 067	4298	26 079	10 860				
Empagliflozin costs (€/y)	0	1029			0	1287	0	1029				
Total medication costs (€/y) (%change)	24 134	25 163 (+4%)			12 067	5584 (−54%)	26 079	11 890 (−54%)				
Hospitalizations costs (€/y) (ICU admissions cost €/y)	14 766 (0)	8346 (0)			0 (0)	0 (0)	0 (0)	0 (0)				
Emergency room visits costs (€/y)	1813	518			0	0	0	0				
Ambulance rides costs (€/y)	885	0			0	0	0	0				
Total cost (€/y) (%change)	41 598	34 027 (−18%)			12 067	5584 (−54%)	26 079	11 890 (−51%)				

Note: All participants were included before in the cohort study by Grünert et al.[6] For the pharmacoeconomic outcome calculations, the Dutch cost prices were used as described in Supplementary file 2: Acute ambulance ride €613; Scheduled ambulance ride €272; Emergency room visit €259; Hospitalization academic hospital €642; Empagliflozin 10 mg tablet €1.41; Empagliflozin 25 mg tablet €1.45; G-CSF 0.5 mL syringe 600 μg/mL €66.12; G-CSF 1 mL vial 300 μg/ml €71.45.

Abbreviations: BE, before empagliflozin treatment; d, day; G-CSF, granulocyte-colony stimulating factor; ICU, intensive care unit; I.N.A, information not available; n/a, not applicable; PCDAI, pediatric Crohn's disease activity index (Hyams et al.[12]), ≥30 = moderate/severe disease; clinical response (moderate/severe disease improving to mild/inactive) was best reflected by a decrease in PCDAI of ≥12.5 points; QoL, quality of life; UE, under empagliflozin treatment; y, year.

TABLE 2 General characteristics, patient-reported outcomes, clinical, and pharmacoeconomic outcomes before/under empagliflozin (UCHS).

General characteristics	Participant VII (PT1 in Wortmann et al.[5])		Participant VIII		Participant IX, (PT2 in Wortmann et al.[5])		Participant X		Participant XI	
Country of residence	Austria		Austria		Austria		Germany*		Austria	
Sex	F		F		F		F		F	
Date of start empagliflozin treatment (dd-mm-yyyy)	23-04-2019		14-05-2019		09-07-2019		22-11-2021		03-12-2019	
Age at start empagliflozin treatment (y, m)	21		16		2, 6		0, 4		6, 0	
SLC37A4 variants										
Nucleotide change (NM_001164277.2)	c.359dup		c.359dup		c.1042_1043del		c.1015G > T		c.59G > A	
	c.547 T > C		c.547 T > C		c.1042_1043del		c.1243C > T		c.59G > A	
Predicted protein change (NP_001157749.1)	p.(C121Mfs*10)		p.(C121Mfs*10)		p.(L348Vfs*53)		p.(G339C)		p.(G20D)	
	p.(C183R)		p.(C183R)		p.(L348Vfs*53)		p.(R415*)		p.(G20D)	
Patient reported outcomes	**BE**	**UE**	**BE**	**UE**	**BE**	**UE**	**BE**	**UE**	**BE**	**UE**
QoL Score (Scale 0–10)	2	8	I.N.A.	I.N.A.	I.N.A.	NA	I.N.A.	9	5	10
Clinical outcomes										
G-CSF (ug/kg/d)	46	0	32	0	10.2	0	33	0	15	0
Empagliflozin (mg/kg/d)	0	0.4	0	0.3	0	0.3	0	0.3	0	0.3
Neutrophil count (10^9/L)	0.3	0.4	0.3	4.7	2.6	6.1	1.0	1.5	0.7	2.0
Hemoglobin (mmol/L)	8.4	9.2	9.4	12.6	10.7	12.4	9.7	14.2	9.0	14.0
(P)CDAI°	221	94	30	109	10	2.9	0	0	12.5	10
Hospital (ICU) admissions /y*	23 (3)	8 (1)	11	0	32	12	26	3	5	7 (2)
Emergency room visits/y	2	0	21	0	5	0	0	1	0	1
Ambulance rides/y	0	0	0	0	1	0	0	1	0	0
Outpatient clinic visits/y	2	2	3	3	6	3	14	2	1	3
Primary care visits/y	7	6	6	6	n.a.	n.a.	11	9	2	2
Pharmacoeconomic outcomes										
G-CSF vial cost (€/y)	19 809	0	16 932	0	8466	0	19 809	0	8466	0
Empagliflozin cost (€/y)	0	934	0	934	0	234	0	156	0	467
Total medication cost (€/y) (%change)	19 809	934 (−95%)	16 932	934 (−94%)	8466	234 (−97%)	19 809	156 (−99%)	8466	467 (−94%)
Hospitalizations cost (€/y) (ICU admissions cost €/y)	19 166 (6777)	10 454 (2259)	9583 (0)	0 (0)	27 878 (0)	10 454 (0)	21 780 (0)	2614 (0)	3485 (0)	5227 (4518)
Emergency room visits cost (€/y)	458	0	687	0	1145	0	0	229	0	0
Ambulance rides cost (€/y)	0	0	0	0	107	0	0	107	0	0
Outpatient clinic visits cost (€/y)	458	458	687	687	1603	687	3206	458	229	687
Total cost (€/y) (%change)	46 668	14 106 (−70%)	27 889	1392 (−95%)	39 200	11 376 (−71%)	44 795	3564 (−92%)	12 180	10 899 (−11%)

Of note, the budget impact probably underestimates the real life costs as only medication costs and costs of medical consultations were calculated. We could not quantify costs of the full cycle of care, productivity loss by families, and handling costs associated with providing medication. **Social value** is likely generated by several factors, such as reduction in productivity loss (e.g., absence from work or school), enabling individuals with GSDIb and their family members to be more engaged in their social and professional lives.

This analysis demonstrates that empagliflozin can improve **personal value** for persons with GSDIb and their caregivers. QoL scores showed a marked increase during empagliflozin treatment. The greatest benefits were reported in terms of improved eating (see quotes in Supplementary file 3), reduction of the painful G-CSF injections, and lower frequency and severity of mucocutaneous lesions. Importantly, some anecdotes emphasized that empagliflozin can be highly individualized, as it improved specific elements unique to the characteristics and preferred lifestyles of these individuals, that would not have been captured by general QoL instruments. For instance, participant VI stated the inconvenience associated with the need to keep G-CSF refrigerated when traveling, and participant VII emphasized that empagliflozin enabled her to get dental braces which was previously not deemed possible due to the risk of infection and gingival problems.

In line with preceding studies (in which several of our participants described here were included),[5,6,20,21] we demonstrate positive effects of empagliflozin on clinical outcomes in GSDIb (**technical value**), such as the gastrointestinal and mucocutaneous symptoms, as reflected by clinical scoring systems (e.g., (P)CDAI) and laboratory results (e.g., absolute neutrophil count, hemoglobin). It is important to emphasize that the neutrophil counts do not always normalize but the clinical diagnosis of a normalized neutrophil function should guide and allow the cessation of G-CSF. The authors expect that as experience with this new treatment increases, more GSDIb individuals will discontinue G-CSF.

Empagliflozin is developing as the most rational first line pharmacotherapeutic treatment option for newly diagnosed, mostly pediatric, GSDIb individuals with signs and symptoms of neutropenia and neutrophil dysfunction. Therefore, we have systematically applied the benefit–risk analysis for off-label use of empagliflozin in GSDIb, according to the BRAvO framework.[19] The benefits of empagliflozin in GSDIb clearly outweigh the risks, when balancing the pathomechanism-based treatment of empagliflozin and its alternative G-CSF, and the possible side effects of these treatments. Our structured benefit–

Note: All participants were included before in the cohort study by Grünert et al.[6] For the pharmacoeconomic outcome calculations, the Austrian cost prices were used as described in Supplementary file 2: Acute ambulance ride €107; Emergency room visit €559; Hospitalization academic hospital €871.20; Hospitalization intensive care unit €2259; Outpatient clinic visit €220; Empagliflozin 10 mg tablet €1.28; Empagliflozin 25 mg tablet €1.28; G-CSF 1 mL vial 300ug/ml €54.20.

Abbreviations: BE, before empagliflozin treatment; CDAI (Best et al.[13]), (0–600, severe >450, remission <150); d, day; G-CSF, granulocyte-colony stimulating factor; ICU, intensive care unit; I.N.A., information not available; n/a = not applicable; PCDAI, pediatric Crohn's disease activity index (Hyams et al.[12]), ≥30 = moderate/severe disease; clinical response (moderate/severe disease improving to mild/inactive) was best reflected by a decrease in PCDAI of ≥12.5 points; QoL, quality of life; UE, under empagliflozin treatment; y, year. *, Participant X lives in Germany but receives all health care in AT.

TABLE 3 Budget impact analysis for 25 mg/day empagliflozin in persons with GSDIb in two nationwide scenarios.

			The Netherlands		Austria	
		Formula	Scenario 1	Scenario 2	Scenario 1	Scenario 2
A	GSDIb persons (*n*)		18[a]	18[a]	12[b]	12[b]
B	GSDIb persons depending on G-CSF before empagliflozin (*n*)		6[c]	17[d]	4[c]	12
C	G-CSF costs per GSDIb person before empagliflozin per year (€)		26 079	26 079	19 783	19 783
D	G-CSF costs per year (€)	[B × C]	156 476	433 347	79 132	237 396
E	G-CSF costs per 3 years (€)	[3 × B]	469 427	1 330 042	237 396	712 188
F	Empagliflozin (25 mg/day) costs per GSDIb person per year (€)		529	529	467	467
G	GSDIb persons stopping G-CSF under empagliflozin (*n*)		3[e]	9[e]	2[e]	12[f]
H	G-CSF cost savings per year (€)	[C × G]	78 238	234 713	39 566	237 396
I	G-CSF cost savings per 3 years (€)	[3 × H]	234 713	704 140	118 698	712 188
J	Budget impact empagliflozin per year (€)[g]	[B × F]	3176	8997	1869	5606
K	Budget impact empagliflozin per 3 years (€)[g]	[3 × J]	9527	26 992	5606	16 819
L	Total cost savings per year (€)[g]	[H−J]	75 062	225 716	37 697	231 790
M	Total cost savings per 3 years (€)[g]	[I−K]	225 187	677 148	113 092	695 369

Note: For calculations, the cost prices were used as described in Supplementary file 2. The following sources and assumptions were made: a, based on DDRMD; b, based on the Austrian national registry for inborn metablic diseases[15]; c, based on Visser et al.[16]; d, based on the historical cohort of GSDIb patients at the UMCG, where 17 out of 18 (93%) used G-CSF; e, based on Grünert et al.[6]; f, Based on the UCHS cohort of GSDIb patients, who all stopped G-CSF under empagliflozin; g, this includes an assumption that there is no clinical indication for empagliflozin in GSDIb patients who are not on G-CSF.

TABLE 4 Sensitivity analysis of total annual medication costs before and under empagliflozin in a theoretical 33 kg person with GSDIb, in different literature based scenarios.

			Total annual medication costs per person year (365 days) in €			
Scenarios	**G-CSF**	**Empagliflozin**	**The Netherlands**		**Austria**	
	(ug/kg/day)	*(25 mg/day)*	*G-CSF vial discarded*	*Exact G-CSF dose*	*G-CSF vial discarded*	*Exact G-CSF dose*
1. Dale et al.[2]	3.0	No	26 079	8606	19 783	6528
2. Wortmann et al.[5]	7.5	No	26 079	21 515	19 783	16 321
3. Grünert et al.[6]	4.0	No	26 079	11 475	20 250	8705
4. Wortmann et al.[5]	0.6	Yes	26 609	2780	20 250	1773
5. Grünert et al.[6]	1.7	Yes	26 609	5935	20 250	4166
6. This study (difference between scenario 1 and 6)	No	Yes	529 (−98%)	529 (−94%)	467 (−98%)	467 (−93%)

Note: For calculations, the cost prices were used as described in Supplementary file 2.

risk analysis may generate additional **allocative value** (i.e., equitable distribution of resources across all affected individuals according to the personal and medical needs) by paving the way toward disseminating this specific indication via (national) pediatric formularies, such as the Dutch "Kinderformularium" (https://kinderformularium.nl) and its Austrian version (www.kindermedika.at), among others.

The role of the academia in drug repurposing for rare diseases is gaining attention and a framework for the repurposing of established medicines has been developed in the European Union.[22,23] Empagliflozin is well-established and safe in its current areas of usage.[24–26] According to an international questionnaire study, empagliflozin treatment was reimbursed in 78% of the cases, but mostly on an individual basis, depending on

individual agreements with either the hospital or health insurance company.[7] In both the Netherlands and Austria, off-label prescriptions are not automatically reimbursed and reimbursement is only possible following assessment by national health insurance organizations—upon request by the manufacturer or healthcare professionals, supported by evidence. Another option for repurposed drugs is authorization of the novel indication (i.e., the on-label route), but this expensive and lengthy process is often not feasible for ultra-rare indications such as GSDIb, with very small market potential.[27,28]

Our study clearly demonstrates that reimbursement of empagliflozin by national authorities and health insurance companies would not only save costs and improve quality of life, but also generate increased **personal value** and **technical value**, compared to the former/presumed standard of care with G-CSF monotherapy. While a VBHC approach is of interest to show the impact of empagliflozine, we argue that its pricing should be cost-based and reflect actual investments. When applied for value-based pricing, prices will increase dramatically, which will jeopardize that same cost-effectiveness and impede a fair distribution of resources.

Some limitations of our study need to be discussed. First, this study has a relatively short follow-up period and no formal cost-effectiveness analysis was carried out. However, the overall cost reduction is clear. Second, due to the retrospective study design possible recall bias for data collected via interviews must be taken into account. This may result in a discrepancy of QoL rating by participants when reflecting back compared to rating at the given time. However, based on our clinical experience, the overall positive reports by participants and care takers are trustworthy reflections. Third, non-hospital related medical costs and indirect costs of decreased labor productivity by caregivers were not included, which has underestimated the total cost reduction by empagliflozin. Lastly, collection of real-world derived data cannot be expected to be seamless due to the retrospective study design and multiple health care providers involved in the care for persons with GSDIb. The authors realize that the study is performed in two western European countries; outcomes may be different in other or developing countries with different healthcare systems.

In summary, we demonstrated that off-label empagliflozin treatment in GSDIb generates additional value at multiple VBHC pillars. Empagliflozin improves personal and clinical outcomes for persons with GSDIb and their caregivers, while reducing costs. This study adds to the evidence supporting use of empagliflozin as standard of care for GSDIb, which should support reimbursement.

AUTHOR CONTRIBUTIONS

Conceptualization: MSB, HG, CEMH, SBW, and TGJD. *Funding Acquisition*: AV, CK, SBW, and TGJD. *Project Administration*: AV and CK. *Data Curation*: AV, CK, SBW, and TGJD. *Formal Analysis*: AV, CK, EB, SBW, and TGJD. Investigation: AV, CK, EB, SBW, TGJD. Writing—original draft: AV, CK, SBW, and TGJD. *Writing—review and editing*: all authors. Correspondence: TGJD and SBW. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. All authors confirm the absence of previous similar or simultaneous publications.

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CONFLICT OF INTEREST STATEMENT

TGJD declares that he experiences no competing interests concerning the content of this manuscript. However, there are confidentiality agreements with third parties. In the past 36 months, there have been consultation agreements (with Danone, Ultragenyx Pharmaceutical Inc, ModernaTX Inc, and Beam Therapeutics), contracts for financial research support for investigator-initiated research (NCT04311307) and sponsor-initiated research (NCT03517085, NCT03970278, NCT05139316, and NCT05196165), honoraria for lectures or presentations (by MEDTalks, Prelum, and Danone), and participations in a Data Safety Monitoring Board (NCT05095727) and Advisory Boards (Ultragenyx Pharmaceutical Inc, ModernaTX Inc, and Beam Therapeutics). For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG. AV, CK, and EB have no conflicts of interest. RJO declares that he experiences no competing interests concerning the

content of this manuscript. There is a consultation agreement (with Ultragenyx Pharmaceutical Inc) of which the contract is via UMCG Contract Research Desk and all payments are to UMCG. NNS, MSB, ELC, FE, HG, and CEMH have no conflicts of interest. SBW declares that over the last 3 years in the area of inherited metabolic diseases she has received accommodation support from Nutricia Metabolics.

DATA AVAILABILITY STATEMENT

Data are available from the authors on reasonable request.

ETHICS STATEMENT

In the Netherlands, the off-label empagliflozine treatment in GSDIb patients was performed according to the guideline of the Royal Dutch Medical Association, which implies written informed consent and prior consultation with the hospital pharmacist. The Medical Ethical Committee of the UMCG (METc 2019/119) and UCHS stated that the Medical Research Involving Human Subjects Act (in Dutch abbreviated as WMO) was not applicable and that official study approval was not required for this retrospective, non-interventional study. Adult participants >16 years of age, and parents or legal guardians on behalf of their children <12 years of age (ages based on Dutch Law, that is, The Dutch Medical Treatment Contracts Act, abbreviated as WGBO) made a voluntary and active contribution to the study by participation in the interviews.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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