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Towards sustainability and affordability of expensive cell and gene therapies? Applying a cost-based pricing model to estimate prices for Libmeldy and Zolgensma

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ABSTRACT

Background aims: Drug prices are regarded as one of the most influential factors in determining accessibility and affordability to novel therapies. Cell and gene therapies such as OTL-200 (brand name: Libmeldy) and AVXS-101 (brand name: Zolgensma) with (expected) list prices of 3.0 million EUR and 1.9 million EUR per treatment, respectively, spark a global debate on the affordability of such therapies. The aim of this study was to use a recently published cost-based pricing model to calculate prices for cell and gene therapies, with OTL-200 and AVXS-101 as case study examples.

Methods: Using the pricing model proposed by Uyl-de Groot and Löwenberg, we estimated a price for both therapies. We searched the literature and online public sources to estimate (i) research and development (R&D) expenses adjusted for risk of failure and cost of capital, (ii) the eligible patient population and (iii) costs of drug manufacturing to calculate a base-case price for OTL-200 and AVXS-101. All model input parameters were varied in a stepwise, deterministic sensitivity analysis and scenario analyses to assess their impact on the calculated prices.

Results: Prices for OTL-200 and AVXS-101 were estimated at 1 048 138 EUR and 380 444 EUR per treatment, respectively. In deterministic sensitivity analyses, varying R&D estimates had the greatest impact on the price for OTL-200, whereas for AVXS-101, changes in the profit margin changed the calculated price substantially. Highest prices in scenario analyses were achieved when assuming the lowest number of patients for OTL-200 and highest R&D expenses for AVXS-101. The lowest R&D expenses scenario resulted in lowest prices for either therapy.

Conclusions: Our results show that, using the proposed model, prices for both OTL-200 and AVXS-101 lie substantially below the currently (proposed) list prices for both therapies. Nevertheless, the uncertainty of the used model input parameters is considerable, which translates in a wide range of estimated prices. This is mainly because of a lack of transparency from pharmaceutical companies regarding R&D expenses and the costs of drug manufacturing. Simultaneously, the disease indications for both therapies remain heavily understudied in terms of their epidemiological profile. Despite the considerable variation in the estimated prices, our results may support the public debate on value-based and cost-based pricing models, and on "fair" drug prices in general.

Introduction

Cell and gene therapies (CGTs) are a heterogeneous group of innovative therapies. This group includes gene therapy, somatic cell therapy, and tissue-engineered products and in Europe is formally regulated as advanced therapy medicinal products [1]. CGTs are expected to bring considerable health benefits, particularly for

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indications with a high unmet medical need and diseases previously deemed untreatable. High clinical development activity is observed, and it is expected that 10–20 CGTs per year will undergo assessment for market authorization in the years to come [2]. Given their high reported prices, these novel therapies may pose substantial budget impact and affordability challenges [3].

Spending on pharmaceuticals is increasing continuously in Europe and elsewhere [4–6]. In most countries, it is the responsibility of policymakers to implement strategies to control prices of medicines and to ensure that they are accessible and affordable [7]. In addition to the high prices, health technology assessment bodies and payers have expressed concerns about the timing of payment to impact affordability [8]. The curative potential for chronic indications asks for an upfront payment of costs, which are otherwise spread over multiple years. And, unlike treatment regimens for chronic conditions, one-time therapies cannot be stopped when effects do not match expectations, nor can the costs be recouped.

Two examples of expensive treatments are CGTs such as OTL-200 (brand name: Libmeldy) for the treatment of early-onset metachromatic leukodystrophy (MLD) and AVXS-101 (also known as onasemnogene abeparvovec-xioi, brand name: Zolgensma) for the treatment of spinal muscular atrophy (SMA). Currently, OTL-200 holds centralized marketing authorization in the European Union (EU), but official list prices are not publicly available [9]. In a corporate presentation from the manufacturer (Orchard Therapeutics, hereafter: ORTX), a price range between 2.5 and 3.0 million Euro (EUR) per treatment, however, is anticipated [10]. In 2021, AVXS-101 holds marketing approval in the United States, Japan, and the EU, with quoted list prices of 2.1 million US dollars (USD, approximately 1.8 million EUR), 167 million Japanese yen (approximately 1.3 million EUR), and 1.9 million EUR (in Germany) per treatment. Such highly priced drugs are a concern, as they can jeopardize the affordability of health care systems. And, indeed, for some countries the affordability of novel and expensive therapies is already at risk [11–14].

To safeguard affordability of new therapies, Uyl-de Groot and Löwenberg [15] suggested a novel pricing model for such therapies in which the price is based on costs of research and development (R&D), drug manufacturing, sales, marketing, the eligible patient population and a profit margin for the industry. However, until now, the model has not been applied in the literature and its feasibility has not been determined. Therefore, we used this model to estimate prices for CGTs, and likewise to determine whether the model can be used with currently available evidence. To this end, we took OTL-200 and AVXS-101 as case studies. The results of our calculations may be used in reimbursement negotiations for these therapies. In addition, they may support the public debate on value-based and cost-based pricing models, and on "fair" drug prices in general.

Methods

Pricing model

The cost-based pricing model described by Uyl-de Groot and Löwenberg [15] was used to estimate the prices of two CGTs using OTL-200 and AVXS-101 as case studies. The model combines the costs of R&D (C_{rd}), the number of patients (N_p) who can benefit from the new drug during the time in years left of patent protection, the costs to manufacture the drug (C_{man}) and a profit margin (M_p) to calculate a price for the novel therapy (C_{tx}, see Eq. 1).

$$C_{tx} = \left(\frac{C_{rd}}{N_P} + C_{man}\right) * (1 + M_p) \quad (1)$$

To adhere to the original model methodology, the perspective of this study is set to the "more developed regions" as defined by the United Nations (UN) Department of Economic and Social Affairs (i.e., Europe, Northern America, Australia/New Zealand, and Japan) [16].

Input parameters for the pricing model were extracted from the literature and public online sources. All prices and costs are stated in 2020 EUR and were inflated with the Dutch Consumer Price Index using the R package *cbsodataR* [17], when necessary. For eventual currency conversions (i.e., in case costs or prices were stated in a currency other than EUR) the R package *priceR* was used to retrieve (historical) exchange rates [18].

In the following sections, we briefly describe the general methodology used to estimate the model inputs, outline the key assumptions and state values for the model base-case analysis (see also Table 1) [19–24]. More information on all input parameters can be found in the Appendices.

Estimating costs for R&D (C_{rd})

For this analysis, we sought to estimate expenses for R&D for OTL-200 and AVXS-101 as precisely as possible. To this end, we followed an approach similar to recently conducted study by Wouters *et al.* [19], which received the highest "suitability score" (81 of a maximum of 96) in the review by Schlander *et al.* [25]. The suitability score framework was designed by the authors of the review to assess how comprehensively the included studies identified and incorporated appropriate factors to estimate R&D expenses. This framework includes 16 factors, classified into three domains, with a high suitability score indicating that studies considered and addressed a wider range of factor. Detailed information in this framework can be found in the Appendix of the original publication [25].

In a first step, we reviewed publicly available financial reports from all companies involved in the R&D process of the case studies. Such reports mainly included filings of financial statements that public companies are required to submit to the US Security and Exchange Commission (SEC). Publicly traded firms submit either quarterly of annual filings to the SEC (Forms 10-Q and 10-K, respectively). From these filings, information on R&D expenses were extracted, starting from the year a particular product was first mentioned in the SEC filings or company reports. We refer to all costs taken from the SEC filings and other not already adjusted costs as "out-of-pocket." Furthermore, we distinguished between several stages of pharmaceutical drug development that both therapies underwent until their first marketing approval, namely (i) pre-clinical phase, (ii) phase 1 clinical and (iii) phase 2 clinical. Similar to previous studies, we considered phase 1/2 studies as phase 2 [19,20]. In case R&D expenses for these stages could not be deduced or approximated from the SEC filings, we used lump sum estimates per stage as estimated by Wouters et al. [19].

R&D efforts for OTL-200 and AVXS-101 were done by different companies. OTL-200 was initially researched by GlaxoSmithKline (GSK) and transferred to Orchard Therapeutics plc. (ORTX) through an asset purchase in the third quarter of 2018 [26]. AVXS-101 was first developed by AveXis (AVXS) and added to the product portfolio of Novartis International AG (Novartis) in the second quarter of 2018, after a company acquisition [27].

While bigger companies usually do not report R&D expenses stratified by therapeutic area or even on product level, smaller manufacturers often do so. Indeed, both ORTX and AVXS reported expenditures on R&D in their filings to the SEC. These expenditures included costs for (i) any type of overhead, (ii) employees (i.e., salary, benefits, stock-based compensations), (iii) consultations (i.e., fees, stock-based compensations), (iv) material (i.e., acquisition, developing, manufacturing), (v) studies (i.e., pre-clinical studies, clinical studies), (vi) licenses (up-front payments) and (vii) any type of regulatory approval [26,28]. Following these definitions, we assumed that all relevant R&D expenses for the therapies of two case studies were included. An overview of the sources used to estimate R&D expenses for both case studies is depicted in Figure 1.

Second, we accounted for so-called "abandoned" drugs or "failed projects" [15,19]. Similar to Wouters *et al.* [19], we used development phase-specific success rates published by Wong *et al.* [20] to correct for this (see Table 1). Third, we considered a real cost of capital rate of 10.5%, as done in previous studies [19,29]. Since lump sums reported by Wouters *et al.* [19] already included a success rate adjustment and cost of capital for pre-clinical stages, we adjusted R&D lump sums for phase 1 and phase 2 accordingly.

R&D costs for OTL-200

Estimated R&D expenses for OTL-200 were based on costs made by GSK and ORTX. Since GSK only reported global figures on R&D expenses in all their SEC filings, we assumed lump sum costs for both the pre-clinical phase and phase 2 for GSK (see Table 1) [19]. Expenses for phase 1 were not considered because both safety and efficacy of OTL-200 (formally known as GSK-2696274), were assessed in a phase 1/2 clinical study (NCT 01560182). Lump sum costs for phase 2 were corrected with a cost of capital for the time between the start of clinical trial in April 2010 and the transferal of rights from GSK to ORTX in the third quarter of 2018 (i.e., 8.3 years) [30]. This resulted in total assumed R&D expenses of 488.93 million EUR when capitalized and risk adjusted (sum of pre-clinical and phase 2, out-of-pocket expenditures were 298.22 million EUR), incurred by GSK [19].

Although OTL-200 was already in its registrational phase, we considered further R&D expenses made by ORTX, assuming that R&D efforts continued until first marketing approval was issued. For these expenses, we relied on ORTX's SEC filings. In the annual SEC filings (i.e., 10-K form), ORTX reported R&D expenses for therapeutic areas (i.e., neurometabolic disorder, primary immune deficiencies, blood disorders, as well as other research and pre-clinical programs under development) for the years 2018–2020. For this analysis, we used reported R&D expenses for the therapeutic area of neurometabolic disorders starting from the last quarter in 2018 (i.e., after ORTX had acquired OTL-200 form GSK) until its first marketing approval by the European Medicines Agency (EMA) [31]. Consequently, we assumed total capitalized and risk adjusted R&D expenses for ORTX of 51.28 million EUR (16.29 million EUR out-of-pocket). A detailed calculation can be found in Appendix A (Table 3 and Table 4). [10,32]. Combining all capitalized and risk-adjusted R&D expenses of GSK and ORTX resulted in a total of 540.2 million EUR for OTL-200 (314.51 million EUR out-of-pocket).

R&D costs for AVXS-101

Assumed R&D expenses for AVXS-101 were based on costs made by AVXS and Novartis. In the 2015 annual filing (10-K) to the SEC, AVXS stated that it did not begin R&D activities of AVXS-101 until the year 2013 [28]. Furthermore, all 10-K filings for the years 2015–2018 stated that substantially all of the company's R&D expenses "have been associated with AVXS-101" [28]. Based on this statement, we assumed that all reported R&D expenses by AVXS could be attributed to AVXS-101. AVXS defined R&D expenses similar to ORTX, and a total of 2.87 billion EUR when capitalized and risk adjusted (out-of-pocket expenditure were 0.41 billion EUR) could be attributed to this therapy [28]. An overview of all R&D expenses reported by AVXS can be found in Appendix B (Table 5).

To estimate the remaining R&D expenses for AVXS-101 between AVXS' last SEC filing and the first marketing approval of the product in the United States (May 2019), we estimated average monthly R&D expenses based on the last available SEC filing (AVXS 2018 10-Q form, see Appendix B) [27]. This was done because Novartis acquired AVXS and detailed R&D expenses by product or therapeutic area could no longer be retrieved. In addition, lump sum estimates for a registrational phase were not available from Wouters *et al.* [19]. In total, we added capitalized and risk adjusted R&D expenses of 323.42 million EUR (266.84 million EUR out-of-pocket) for the period between March 2018 and May 2019 to the total R&D expenses, reported by AVXS. This led to a total estimate of R&D expenses of 3.19 billion EUR for AVXS-101 when capitalized and risk adjusted (678.77 million EUR out-of-pocket).

Number of eligible patients during patent protection (N_p)

The number of eligible patients during the remaining patent protection of both products was calculated using incidence and prevalence rates from the literature for MLD (OLT-200) and SMA (AVXS-101). Prevalence rates were multiplied with the population estimation from the 2019 UN Revision of World Population Prospects [33]. These data were taken from the R package wpp2019 [34]. Incidence rates (or more precisely: "birth prevalence rates" in these cases) were multiplied with the estimated number of newborns in the UN more-developed regions. These data were based on yearly interpolated births from the year 2020 onwards (time of marketing approval for OTL-200 and AVXS-101) [35].

Estimating the duration of remaining patent protection

In contrast to Uyl-de Groot and Löwenberg [15], we extended the definition of the "number of patent years after registration" to also include all applicable intellectual property protection (IPP) such as patent protection, or regulatory protection (RP) such as data protection, or market exclusivity (whichever comes last). [36]

For OTL-200, we could only find information on RP with regard to the granted orphan market exclusivity period ending on December 18, 2030 [37]. Reliable figures on further IPP coverage could not be found. For AVXS-101, we retrieved pertinent data from the 2020 SEC filings by Novartis (see Appendix C [Table 6]), stating that the latest regular data protection would be somewhere in 2031 [24]. We assumed that both OTL-200 and AVXS-101 would be covered by IPP or RP for at least 10 years.

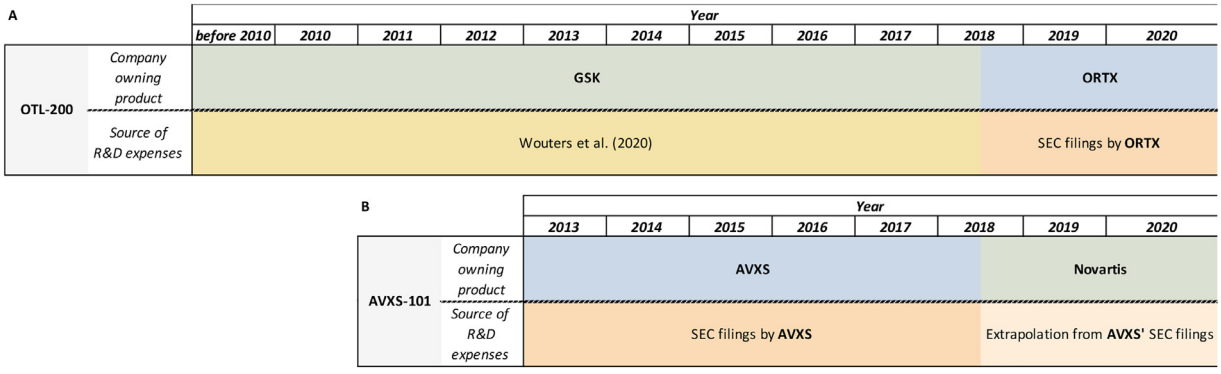

Figure 1. Overview of sources used to estimate R&D expenses for (A) OTL-200 and (B) AVXS-101. R&D, research and development.

Estimating incidence of patients with MLD

In line with current marketing approval of OTL-200 in the EU [9], we only considered an MLD incident population with an average incidence rate of 1.6 per 100 000 newborns, based on the study of van Rappard *et al.* [21]. Furthermore, we restricted the patient population, eligible for OTL-200, to one third because previous studies with comparable therapies in this indication demonstrated that only a fraction of diagnosed patients are eligible for therapy [38]. This choice was validated with clinical experts (see the Acknowledgments). Consequently, we estimated a total of 683 patients with MLD eligible for OTL-200 over a period of 10 years. More details can be found in the Appendix D (Table 7, Table 8, Table 9, Table 10, Table 11).

Estimating incidence and prevalence of patients with SMA

Marketing approval for AVXS-101 differs between the United States, Japan and the EU. While in the United States and Japan AVXS-101 was approved for patients with SMA younger than the age of two years, the EMA did not indicate any age restrictions. Nevertheless, it is mentioned that "[...] there is limited experience in patients 2 years of age and older [...]" [39]. Based on this statement and for this analysis, we assumed that patients above the age of two years, would not receive AVXS-101 in Europe.

Assuming a general age restriction of two years, we considered patients with type I or II SMA to be eligible for AVXS-101. This categorization was based on the literature, and more detail can be found in Appendix D [40–47]. While in theory, the age of onset for SMA type IIIa could be before two years of age, we did not include these patients in our analysis, because a recent study suggested that the minimum age of onset for this type might in fact be later [47].

For our analysis, we relied on SMA-type specific prevalence and incidence rates as summarized in a recent systematic literature review [23]. Consequently, we assumed average prevalence rates of 0.17 per 100 000, and 1.78 per 100 000, for SMA type I and II, respectively. Average assumed incidence rates were 5.77 per 100 000 newborns and 5.89 per 100 000 newborns for SMA type I and II, respectively. These data were used to calculate the total number of patients.

However, due to the explicit age restrictions in the United States and Japan, and the assumed similar age restriction in the EU we only included patients with SMA type II younger than the age of two years. Since no information on the age distribution of patients with SMA type II was available, we approximated this distribution by calculating the proportion of individuals younger than the age of two years in the general population of the UN "more-developed region," which was 3% [33].

To be consistent with the current marketing approval in the United States and Japan, we considered SMA type I and type II for these regions and did not stratify by SMN2 copy involvement. For Europe, we considered all patients with SMA type I and all patients with SMA type II with up to three copies of the SMN2 gene, according to the EMA approval. Information on the distribution of SMN2 copies was taken from the literature [22]. For all other countries fulfilling the more-developed region criteria, we assumed eligible patients similar to the definition of the United States and Japan. The total eligible patient population for AVXS-101 for the base-case analysis were 13 607 patients over a period of 10 years.

Costs of drug manufacturing

Manufacturing costs specific to OTL-200 or AVXS-101 were not available from the SEC filings or the literature. Therefore, we assumed those costs to be similar to the production costs of an adeno-associated virus–mediated factor IX gene therapy. Costs for the latter were estimated through a micro-costing (ingredient list) approach, for a recently published cost-effectiveness analysis [48]. Hence, we assumed 63 477 EUR for the production costs of OTL-200 and AVXS-101 per therapy for one patient. Since manufacturing cost estimates were derived from an academic facility, our model considers an additional 30% margin for sales and marketing costs in addition to the production costs, as suggested by Uyl-de Groot and Löwenberg [15].

Profit margin (M_p)

Uyl-de Groot and Löwenberg [15] suggested that a reasonable profit margin would ideally be linked to the level of clinical benefit.

Table 1
Base case values from the literature to estimate model input parameters.

Type	Description	Value in use	Reference
Development phase-specific success rate	Pre-clinical to approval	13.8%	Same assumption as Wouters *et al.* (2020) [19]
	Phase 1 to approval	13.8%	Wong *et al.* (2019) [20]
	Phase2 to approval	35.1%	Wong *et al.* (2019) [20]
	Phase 3 to approval	59.0%	Wong *et al.* (2019) [20]
	Submission for marketing authorization to approval	83.2%	Wong *et al.* (2019) [20]
Global lump sum costs for R&D phases (all capitalized and risk adjusted)	Pre-clinical[a]	209 439 080 EUR	Wouters *et al.* (2020) [19]
	Phase 1[b]	337 615 565 EUR	Wouters *et al.* (2020) [19]
	Phase 2[c]	252 929 385 EUR	Wouters *et al.* (2020) [19]
MLD	Average incidence rate	1.6 per 100 000 newborns	Van Rappard *et al.* (2015) [21]
SMA	Percentage of patients with SMA with up to three SMN2 gene copies (used to calculate patients in Europe)	94.66%	Calucho *et al.* (2018) [22]
	One copy of *SMN2* gene	0.34%	Calucho *et al.* (2018) [22]
	Two copies of *SMN2* gene	16.55%	Calucho *et al.* (2018) [22]
	Average incidence rate: SMA type I	5.77 per 100 000 newborns	Verhaart *et al.* (2017) [23]
	Average incidence rate: SMA type II	5.89 per 100 000 newborns	Verhaart *et al.* (2017) [23]
	Average prevalence rate: SMA type I	0.17 per 100 000	Verhaart *et al.* (2017) [23]
	Average prevalence rate: SMA type II	1.78 per 100 000	Verhaart *et al.* (2017) [23]
Patent duration	Remaining regulatory or intellectual protection: AVXS-101	10 years	Novartis SEC form: '2020 20-F' [24]
	Remaining regulatory or intellectual protection: OTL-200	10 years	Assumption
Profit margin	Profit margin	20%	Uyl-de Groot and Löwenberg (2018) [15]

MLD, metachromatic leukodystrophy; SMA, spinal muscular atrophy; R&D, research and development; SEC, Securities and Exchange Commission.
[a] Already capitalized and risk adjusted in original source, hence no out-of-pocket could be stated.
[b] Out-of-pocket: 45 690 948 EUR.
[c] Out-of-pocket: 88 778 214 EUR.

To this end, they suggested profit margins of 20%, 30% and 40% for marginal, moderate and high levels of clinical benefit, respectively. However, such a benefit cannot yet fully be determined for either therapy because clinical (long-term) evidence for these treatments is lacking. Therefore, we used an arbitrary profit margin of 20% for the base-case analysis. The impact of a wider range of profit margins (i.e., between 10% and 60%) on the calculated price was examined in the deterministic sensitivity analyses. An overview of base case values for the cost-based pricing model per therapy can be found in Table 2 [49,50].

Deterministic sensitivity and scenario analyses

To test the impact of the different model input parameters and assumptions on the price calculations, we varied parameters in deterministic and scenario analyses. In the deterministic sensitivity analysis, we re-calculated the price for OTL-200 and AVXS-101 by stepwise increasing and decreasing all model input parameters (i.e., C_{rd}, the number of patients who can benefit from the new drug during the time in years left of patent protection, costs to manufacture the drug and M_p) by five steps between the minimum value from the scenario analysis (see below paragraph) and the base-case value, and five steps between the base-case value and the maximum value in from the scenario analysis. The value for each step was calculated by dividing the difference between the minimum (or maximum) value and the base-case value by five.

In scenario analyses, we varied model input parameters for which upper and lower bound estimates could be informed by the literature. For this, we used the base-case estimates as reference points and varied each input parameter step by step, while keeping all other parameters similar to the base-case (see Table 2). In this way, we were able to show a range of realistic cost-based prices for both products. In the absence of reliable R&D expenses for CGTs specifically, we used minimum (i.e., 146 million EUR; 161 million USD) and maximum (i.e., 4.11 billion EUR; 4.54 billion USD) estimates reported in a review by Schlander *et al.* [25] However, using these ranges directly would inflate the margins disproportionally. This is because the review included costly phase 3 trials, many different therapeutic classes and a large variation of drug sample inclusion periods, among other factors. In addition, since both OTL-200 and AVXS-101 were approved based on phase 2 trials with fewer than 25 participants [9,51–53], employing the 4.11 billion EUR estimate for R&D expenses of both products would be too high. Therefore, we chose to determine both minimum and maximum R&D estimates for each therapy based on the 0.05 and 0.95 percentile of a truncated normal distribution. The distribution's mean was the base-case R&D estimate of the respective therapy, whereas values for standard deviation and upper/lower bounds were based on the total range reported by Schlander *et al.* [25]. Hence, by varying only the mean, we received different R&D estimates for each drug, reflecting the relative uncertainty around the base-case estimates (see Appendix E for more information [54,55]). The number of eligible patients for OTL-200 and AVXS-101 was based on minimum and maximum incidence and prevalence rates found in the literature (see Appendix D). Lower estimates for drug manufacturing costs were approximated with a study by ten Ham *et al.* [49] on cell manufacturing costs. Since higher bound estimates for drug manufacturing costs were reported to be underestimations, we added the absolute difference between lower and higher reported estimates to the highest estimate. This resulted in maximum costs for drug manufacturing of 84 333 EUR. Finally, we assumed no profit margin (i.e., 0%) for the lowest possible estimate and 76.5% as highest value, based on Ledley *et al.* [50].

Table 2
Base-case and scenario input values for OTL-200 and AVXS-101.

	OTL-200	AVXS-101
R&D expenses (C_{rd}) in EUR		
Base-case	540 204 057	3 191 067 181
Scenario 1[a]	227 778 464	1 624 092 896
Scenario 2[a]	2 207 848 401	3 959 441 065
Eligible number of patients during patent protection (N_p)		
Base-case	683	13 607
Scenario 3[b]	597	7077
Scenario 4[c]	768	23 626
Cost of drug manufacturing (C_{man}) in EUR[d]		
Base-case	63 477	63 477
Scenario 5[e]	23 033	23 033
Scenario 6[f]	84 333	84 333
Profit margin (M_p) in %		
Base-case	20	20
Scenario 7	0	0
Scenario 8[g]	76.5	76.5

C_{man}, cost of drug manufacturing; C_{rd}, cost of research and development; EUR, Euro (currency); M_p, profit margin N_p, number of patients; R&D, research and development.

[a] Estimated from a truncated normal distribution assuming the base-case R&D estimate per drug as the mean; standard deviation and upper/lower bounds are based on Schlander *et al.* [25] (see Appendix E)

[b] Based on minimum reported incidence and prevalence rates (see Appendix D)

[c] Based on maximum reported incidence and prevalence rates (see Appendix D)

[d] This does not include a 30% margin for sales and marketing, which is added in the model calculations

[e] Based on the minimum reported value in ten Ham *et al.* (2020) [49]

[f] Based on maximum reported value (53,683 EUR) in ten Ham et al. (2020) and adding the absolute difference between lowest and highest reported values (i.e. 30,650 EUR) because ten Ham et al. argued that the maximum value was likely to be an underestimation of the real costs

[g] Based on maximum reported value in Ledley *et al.* (2020) [50]

Results

With the input values presented in Table 2, the model proposed by Uyl-de Groot and Löwenberg [15] (Eq. 1) results in an estimated base-case price of 1 048 138 EUR and 380 444 EUR per treatment and patient, for OTL-200 and AVXS-101, respectively. The results of the deterministic sensitivity analysis are summarized in Figure 2. The deterministic sensitivity analysis showed that the variation of the model input parameters had different effects on the calculated total price of either case study. For instance, assuming higher R&D expenses for OTL-200 resulted in a substantial increase of the calculated price, whereas increasing assumed R&D expenses for AVXS-101 had a relatively smaller effect on the price. In addition, it can be seen that R&D expenses have the most impact on the price calculated for OTL-200, whereas for AVX-101 increasing the assumed profit margin causes the highest price increase, followed by assuming less-eligible patients. All input parameters and the results of the deterministic sensitivity analysis can be found in Appendix F (Table 12).

The results of the different scenario analyses (see Figure 3 and Appendix G [Table 13]) show that the highest price for both OTL-200 (i.e., 3 978 114 EUR) and AVXS-101 (i.e., 640 112 EUR) were achieved when assuming the highest R&D expenses for OTL-200 and assuming the lowest number of patients for AVXS-101. Furthermore, the lowest price for OTL-200 (i.e., 499 221 EUR) and AVXS-101 (i.e., 242 253 EUR) resulted from assuming the lowest R&D expenses.

Considering both deterministic sensitivity and scenario analyses, the price range for OTL-200 was between 499 221 EUR and 3 978 114 EUR, with a base-case point estimate of 1 048 138 EUR. In comparison, the price range for AVXS-101 was narrower with prices between 242 253 EUR and 640 112 EUR, and a base-case point estimate of 380 444 EUR. When only out-of-pocket R&D expenses were considered, the estimated drug prices were 651 596 EUR and 158 885 EUR for OTL-200 and AVXS-101, respectively.

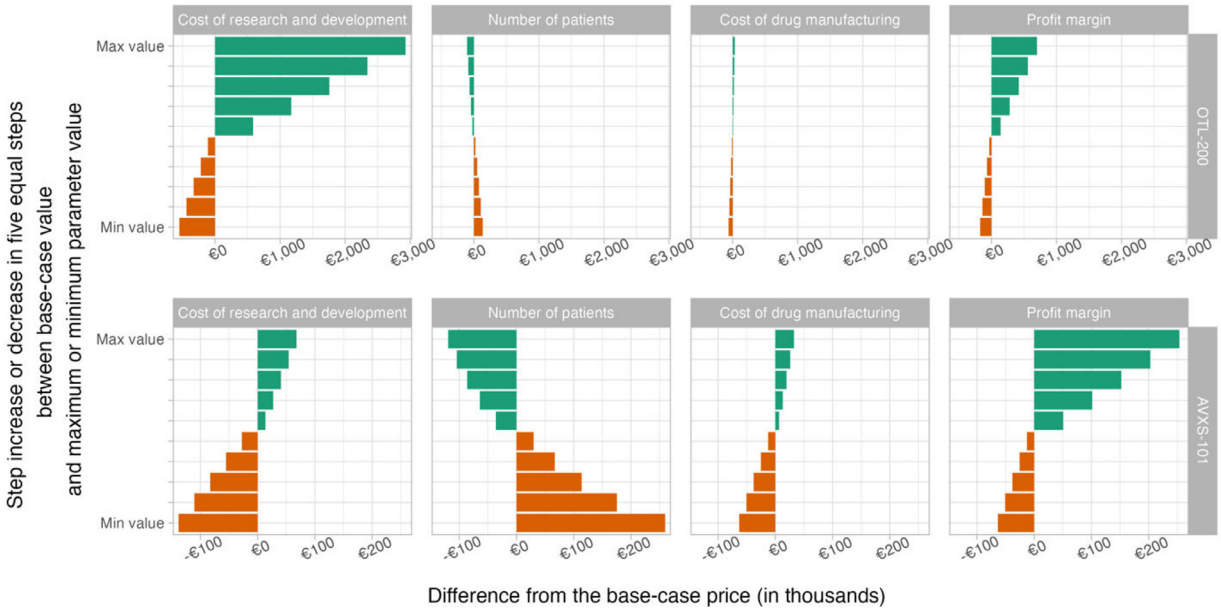

Figure 2. Results of the deterministic sensitivity analysis.

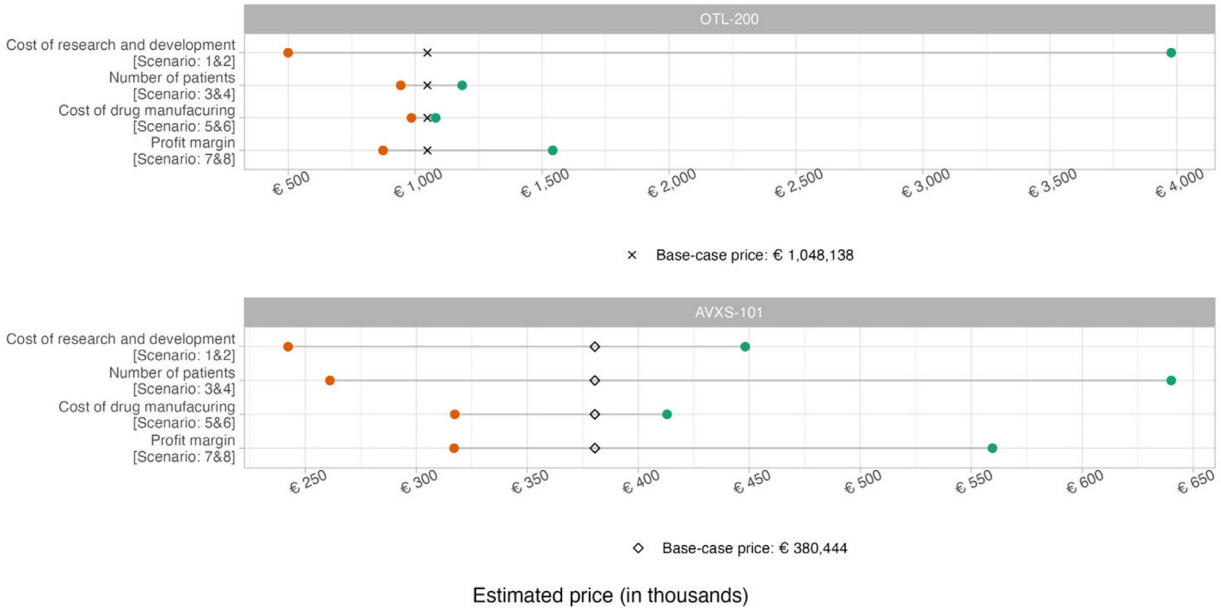

Figure 3. Results of the scenario analyses.

Discussion

In this study, we meticulously estimated all necessary input parameters to calculate drug prices for OTL-200 and AVXS-101 using the pricing model suggested by Uyl-de Groot and Löwenberg [15]. All model input parameters were based on publicly available evidence and R&D expenses were adjusted based on current methodological approaches. The calculated prices for OTL-200 and AVXS-101 were 1 048 138 EUR and 380 444 EUR per treatment, respectively. Lowest and highest prices in deterministic sensitivity and scenario analyses ranged between 499 221 EUR to 3 978 114 EUR per patient and treatment for OTL-200 and 242 253 EUR to 640 112 EUR for AVXS-101. Our deterministic sensitivity analyses demonstrated that a variation of the input parameters (i.e., increase or decrease) had distinct effects on the price outcome. Similarly, when assuming both minimum and maximum values of input parameters in scenario analyses, the estimated prices changed considerably. Nevertheless, most calculated prices in this study were substantially lower than the currently (proposed) list prices for either therapy (list price for OTL-200: between 2.5 and 3.0 million EUR; AVXS: approximately 1.9 million EUR).

Cost of R&D (C_{rd})

In recent years, several cost-based pricing models, such as the one from the International Association of Mutual Benefit Societies [56], the “discounted cash flow” model [57,58] or “rate of return pricing” [59] have been suggested to estimate prices for novel drugs. Model input parameters across these models vary but all include at least R&D expenses. This demonstrates the relative importance of this input parameter to all models. While most of these cost-based pricing models use lump sum estimations, we sought to estimate each model input parameter, and particularly R&D expenses, as precisely as

possible for two reasons. First, because the original published model by Uyl-de Groot and Löwenberg [15] also used actual costs rather than lump sums for their example calculations. Second, the two selected case studies (i.e., OTL-200 and AVXS-101) were partly developed at smaller companies that reported their R&D expenses rather detailed in their pertinent SEC filings.

The deterministic sensitivity analysis showed that the assumed R&D expenses can have a tremendous impact on the calculated price, especially when the number of eligible patients is low. This exhibits the relative importance of knowing the true value of the R&D expenses when using the pricing model. Since both ORTX and AVXS (partly) reported R&D expenses (for OTL-200 and AVXS-101, respectively) in their SEC filings, we believe that we indeed could approximate the total expenses precisely.

Our estimated R&D expense estimations for OTL-200 (i.e., 540 million EUR) and AVXS-101 (i.e., 3.19 billion EUR) fall within the range of expenses reported in the literature. In a recent systematic review of the literature, Schlander *et al.* (2021) reported that R&D expense estimates ranged between approximately 146 million EUR (161 million USD) to 4.11 billion EUR (4.54 billion USD) [19,25,60]. Even the most extreme values explored in our deterministic sensitivity analysis are covered by this range. Nevertheless, all assumed R&D expenses of the base-case, remain at a the low- to mid-range of the reported spectrum in the literature. This may be due to diverging definitions of R&D expenses in the literature and those used by ORTX and AVXS for the SEC filings. For the latter two for instance, it seems that costs for abandoned drugs were not included. In our analysis, R&D estimates for OTL-200 included a success rate adjustment of costs of capital for the pre-clinical phase at GSK. This is because the used lump sum estimates for this development period, estimated by Wouters *et al.* [19], already included these items. While there is no reliable way to precisely estimate additional costs for abandoned drugs [25], we believe that such costs are not applicable to AVXS-101. This is mainly because AVXS was founded in the same year it started researching AVXS-101 (i.e., 2013) and had devoted all of its R&D expenses to this therapy at least until 2018 [28].

Accounting for cost of capital and applying a success rate adjustment to the R&D expenses found in the SEC filings or the literate increased the original expenses substantially. While this has an equally large influence on the calculated cost-based price, it is reasonable to include this adjustment because manufacturers and investors also account for those in their day-to-day business and investment decisions. Estimating a cost-based price without such parameters would not yield a realistic result that can be used for policy purposes in a competitive market. For instance, a report from 2019 calculated that industry-wide, 53% of spending on R&D is lost in cost of capital, 40% on out-of-pocket failure costs and only 7% on out-of-pocket success costs [61]. Without risk and cost of capital adjustments, prices for OTL-200 and AVXS-101 would nearly be half the currently estimated prices (i.e., 651 596 EUR and 158 885 EUR, respectively).

It needs to be noted that all assumed R&D expenses in this study neglect other indirect public (financial) contributions towards the development of OTL-200 and AVXS-101. This choice was made because the proposed pricing model does not define how to account for these contributions and because estimating those will add additional uncertainty to the numbers employed in this analysis. Other studies have found that such public investments may significantly impact the total assumed R&D expenses and even exceed the manufacturer's investment by a factor of 1.5–5.1 [62]. To estimate the total value of public investments for the orphan drug bedaquiline, Gotham *et al.* [62], for instance, considered orphan drug tax credits (ODTCs), priority review vouchers (PRVs), drug-donation programs and publicly funded clinical trials.

Under the US Orphan Drug Act, manufacturers may be eligible for an ODTC for up to 25% (or 50% before the year 2017) of qualified clinical testing expenses. Claiming the ODTC tax credit affects the company's eligibility for (parts of) the regular R&D tax credits and hence the incremental gain of using an ODTC will be lower than 25%. In addition, the impact of ODTCs on lowering costs for developing new treatments for rare diseases seems to be affected by the type of company claiming the ODTC. Especially newer, pre-market developers without previous drug approval will not be able to use ODTCs until they have tax liability that could be reduced by the credit, which can take more than 12 years [63]. However, since ODTCs are transferrable, pre-market companies owning ODTCs may be more attractive for potential mergers and acquisitions with established companies [63,64]. Gotham *et al.* [62] estimated total ODTC (using a 50% rate) value of 22 million USD to 36 million USD for a duration of seven years and across 15 trials. Hypothetically deducting these costs from our estimated R&D expenses would be covered by the range calculated in scenario 1.

On the contrary, if the value of PRVs would need to be deducted from the total R&D expenses could affect the results more significantly. Depending on several factors (e.g., approval acceleration in months and fifth-year sales of the therapy), values of PRVs were estimated to range between 28 million USD to 691 million USD [65]. However, accounting for such PRVs remains a methodological choice associated with quite some uncertainty. First, companies may use acquired PRVs on different, future Food and Drug Administration (FDA) submissions. Second, PRVs can be sold at any time to other companies. Hence, redeeming or selling PRVs would theoretically decrease R&D expenses, which would lead to a lower price. As of 2021, ORTX did not possess a PRV for OTL-200, although one may be granted upon future FDA approval [36]. For AVXS-101, the FDA did issue a PRV to AVXS in 2019, but it is unclear how this was or will be used [66]. Finally, regarding drug-donation programs and publicly funded trials, we could neither find information on those for OTL-200 nor for AVXS-101.

For the development phase-specific success rate factors, we relied on previously published aggregate data. Generally, these success rates increase with advanced clinical phases, and phase 3 trials are conducted before marketing approval. Consequently, the latest conducted phase (i.e., mostly phase 3) also presents with the most favorable success rate of more than 50%. However, in the case of OTL-200 and AVXS-101, the latest conducted phases before marketing approval were phase 2 studies (and not phase 3 studies). If, from the start of drug development, it could have been anticipated that a phase 2 study is sufficient for marketing approval, using a success rate of 35.1% for both case studies might be an underestimation of the true success rate. With an increasing success rate, the R&D expenses for this phase would decrease, which would in turn lead to a decrease in the estimated price for the therapy.

Earlier research suggested that development costs for orphan drugs can differ from development costs for non-orphan drugs [67]. This could warrant an adjustment of the assumed global lump sum costs of clinical studies here. However, this was not done because the average cost estimates used in this study were based on a sample that already contained a large proportion of orphan drugs [19].

Number of eligible patients during patent duration

The total number of eligible patients in the model is related to the remaining duration of IPP or RP. With a longer-lasting IPP or RP, more patients become eligible. Prices for OTL-200 and AVXS-101 were calculated for the study year 2021, which impacted the estimated time remaining with IPP or RP. The deterministic sensitivity analysis showed that an increase in the number of eligible patients had a substantial impact on the calculated price, particularly when the patient population is rather small (as for MLD). The magnitude of this effect was different for both therapies. For instance, increasing the patient population eligible for OTL-200 by 200% resulted in a

price decrease of 46%, while for AVXS-101 the same increase of patients resulted in a price decrease of 4%.

Making a clear distinction between patents and other protection such as orphan drug designation as well as data and market exclusivity might become of particular importance for CGTs. This is because many therapies rely on the same fundamental technologies (i.e., vector or lentiviral technology) and licensing such patent becomes increasingly common. While underlying patents of such technologies seem to be heavily under attack from several parties using the European Patent Office's opposition procedure, legally challenging an orphan drug designation is much more complicated [68].

Generally, information on IPP or RP duration is difficult to retrieve. Even databases such as "DrugPatentWatch" did not include information on the therapies studied here [69]. Simultaneously, original patent holders seem to be reluctant to share information on which patents are licensed for particular products or therapies [70].

For the model calculations, the number of eligible patients also was determined by the epidemiological data used in this study. While epidemiological studies on disease incidence and prevalence generally provide a reliable overview, data for indications targeted by CGTs are scarce. Many indications for CGTs are complex and not yet fully understood. For instance, most epidemiological studies on SMA types are considered outdated, as they typically relied on clinical rather than genetic disease diagnosis [23].

Incidence and prevalence rates based on genetic screening would most likely reveal an underestimation of total assumed eligible cases for our analysis. Consequently, an increase in the patient population would lead to decrease in the estimated price of AVXS-101 based on the pricing model. In some European countries such as the Netherlands, SMA carrier screening as part of a newborn screening are currently planned but not yet implemented [71]. Once newborns will routinely be tested, patients can be diagnosed and treated earlier. This would increase the total eligible patient population for many genetic conditions.

For this analysis, we did not consider factors such as market penetration rates and the possibility that novel, more effective drugs for the same indication might be launched before the IPP or RP expires. Such scenarios would impact the number of eligible patients but are not part of the original pricing model. Including assumptions on market penetration such as 45% in the first and 90% in the second year [72,73], may increase the calculated prices through lowering estimates of the patient population. CGTs will most likely never reach 100% coverage due to reasons such as the availability of non-CGT products, individual preferences of using or prescribing novel therapies, or payer-imposed access restrictions [72]. Currently, the price model does not correct for this. If and when novel, more-effective therapies will enter the market prior to the IPP or RP expiration cannot be known reliably. Since the aim of this study was to apply the model by Uyl-de Groot and Löwenberg [15] using currently available evidence, we based our estimates on the number of eligible patients on the literature. We did not speculate on scenarios that would limit or extend this number based on an arbitrary time before or after patent expiration. Hence, the pricing model cannot precisely account for such scenarios.

Cost of drug manufacturing (C_m)

Compared with more conventional medicinal products, such as small molecules and biologics, the manufacturing of CGTs is a complicated process with distinct challenges [74]. This complexity can be attributed to their specific characteristics. For instance, batches often are personalized for individual patients, manufacturing processes are often manual and starting materials are scarce as well as costly [75–78]. In addition, upfront investment and risk associated with designing and maintaining Good Manufacturing Practice facilities for the production of CGTs are significant [79]. Although biomedical researchers and developers acknowledge the importance of cost and economic consequences of strategic decisions in manufacturing development, little information is available on the cost of CGT manufacturing itself. This, in part can be explained by political sensitivity of publicly disclosing such information. Few studies are available that share lump-sum cost of parts of manufacturing development of very heterogenic CGTs. In needs to be noted that these studies were conducted in public settings such as academia or hospitals [49,80]. It is likely that the actual manufacturing cost of the two case studies differ substantially. For instance, manufacturing costs may decrease over time due to technological advancements. In addition, manufacturers with an extensive CGT portfolio may already have Good Manufacturing Practice facilities at their disposal that can be upscaled or further decentralized [81,82]. To assess the impact of change in manufacturing costs, we varied the model input parameters to account for a wide range (i.e., −50% to +200%). The sensitivity analysis showed that a further decrease in manufacturing costs might lead to a substantial decrease in the estimated drug price and vice versa.

Profit margin (M_p)

Setting a profit margin for the base case analysis was a highly debated item throughout this research. Following the example calculations of Uyl de-Groot and Löwenberg [15], we used the arbitrary profit margin of 20%. We want to highlight that this choice does not reflect any judgment about an acceptable or even "fair" profit margin for the pharmaceutical industry. The selected margin rather reflects the lower spectrum of the actual profit made in this industry. Recently, Ledley *et al.* [50] studied the profitability of 35 large pharmaceutical companies compared with other large public companies between the years 2000 and 2018. Gross profit and EBITDA (earnings before interest, taxes, depreciation, and amortization) margins as a percentage of revenue were 76.5% and 29.4%, respectively [50].

Final remarks and conclusion

This study adds to the existing body of literature on cost-based pricing models by showing how the needed model input parameters could be estimated and what their impact is on the calculated price. In addition, the input parameters used and stated here may facilitate the calculation of cost-based prices for OTL-200 and AVXS-101 with other models to compare their results.

Furthermore, our analysis showed that evidence for most of the model input parameters are scarce and associated with considerable uncertainty. Since variation of each parameter can impact the calculated price substantially, research efforts should focus on eliciting their true values when using this model. While the number of eligible patients can be revealed through epidemiological studies, evidence on R&D expenses and manufacturing costs heavily depend on the information provided by the pharmaceutical industry. There seems to be movement in this debate and the World Health Organization has recently pushed for clearer drug pricing [83,84]. But although the demand for more transparency in setting drug prices and disclosing R&D expenses is growing, it might take years before reliable figures are available [85–87].

With the current uncertainty in most model input parameters, the estimated prices varied considerably. Using the here-presented base-case estimates as benchmarks for OTL-200 or AVXS-101 should therefore only been done with great caution. Also, a setback of cost-based pricing models with the use of case-specific input parameters for R&D costs is that it does not reward efficiency during the R&D process. In this study, this applies more to AVXS-101 than to OTL-200 because for the latter, most R&D costs were estimated using lump sum assumptions from literature. Nevertheless, the results may support the (public) debate on value-based and cost-based pricing models, and on "fair" drug prices in general.

Table 3
Reported expenses for OTL-200 by Orchard therapeutics plc.

Year	Expenses in USD	Expenses in 2020 EUR (converted and indexed)	Source
2018	87 243 000	76 838 072	10-K form 2019
2019	39 042 000	35 317 578	10-K form 2019
2020	17 714 000	15 939 205	10-K form 2020

EUR, Euro (currency); NA, not applicable; R&D, research and development; USD, United States dollars.

Table 4
Estimated R&D expenses for OTL-200 based on SEC filing and share on ORTX's neurometabolic disorder portfolio.

Year	Expenses i n EUR	Assumed share of OTL-200	Risk rate adjustment	Cost of capital	Expenses adjusted for share, time, risk and cost of capital
2018[a]	19 209 518	0.25	35.1%	10.5%	15 118 602
2019	35 317 578	0.25	35.1%	10.5%	27 796 242
2020	15 939 205	0.17	35.1%	10.5%	83 63 163

EUR, Euro (currency); ORTX, Orchard Therapeutics; R&D, research and development.
[a] Here we consider only costs for the last quarter (i.e., three months) of the total R&D expenses made in 2018 because ORTX acquired OTL-200 in that time.

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Author Contributions

Conception and design of the study: FWT, RJSDH, CAU. Acquisition of data: FWT, RJSDH. Analysis and interpretation of data: FWT, RJSDH, SB, RH, CAU. Drafting or revising the manuscript: FWT, RJSDH, SB, RH, CAU. All authors have approved the final article.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

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Appendix A. Estimation of R&D expenses for OTL-200 by Orchard therapeutics plc

An overview of the reported R&D expenses for neurometabolic disorders is presented in Table 3. The 2019 10-K report mentioned a total of nine products in the research pipeline, of which four (25%) targeted neurometabolic disorders [10]. In the 2020 10-K form, this share rose to six of 12 (17%) products [32]. These proportions were used to estimate the R&D expenses share of OTL-200 of all neurometabolic disorders. In the absence of information for the years 2017-2019, we assumed the proportion for these years as for the year 2019 (i.e., 25%). Table 4 summarizes the assumed R&D expenses for OTL-200 in the group of neurometabolic disorders.

Appendix B. Estimation of R&D expenses for AVXS-101 by AveXis

Between 2013 and 2018, AveXis reported total R&D expenses of 2 867 649 241 EUR (including currency conversion, and adjustment for the consumer price index, success rate and cost of capital) in their SEC filings (see Table 5). These costs were used as input for the base-case analysis.

Reported R&D expenses in AveXis' SEC filings were only available until March 31, 2018 because the company entered into an Agreement and Plan of Merger with Novartis (see also Section 3.1.2) [27]. In addition, reported expenses for the first months of 2018 were rather high and had increased by 179 400 000 USD (approx. 158 004 083 EUR) when compared with the same three months in 2017. This increase was primarily due to 135 200 000 USD (approx. 119 075 541 EUR) of expenses recognized pursuant to licenses and agreements with REGENXBIO SMA and Généthon [27]. In addition, R&D expenses increased due to increased spending at the manufacturing facility on materials and supplies, salary and personnel (resulting from increased headcount), process and development (primarily laboratory testing), non-cash stock-based compensation expenses, fixed asset depreciation, payment made to support third party research, rent expense, utilities, and clinical trials.

For this analysis, R&D expenses were considered up to and including the first of marketing approval of AVXS-101in the United States by the FDA in May 2019. Therefore, we extrapolated R&D expenses between the last AveXis SEC filing (i.e., Q-10 in 2018) until May 2019. To this end, we estimated monthly R&D expenses based on the latest available SEC filing of AveXis (i.e., Q-10 in 2018) [21]. This was necessary because after the merger

Table 5
Research and development expenses for AVXS-101 by AveXis.

Year	Stated expenses in USD	Expenses in 2020 EUR (corrected for success rate and including cost of capital)	Clinical phase	Remark	Source
2013	362 609	2 388 304	Pre-clinical		10-K form 2015
2014	13 550 422	168 273 624	Pre-clinical, phase 1	Phase 1 started in April 2014	10-K form 2015
2015	27 493 460	213 224 709	Phase 1		10-K form 2015
2016	58 891 667	456 597 399	Phase 1		10-K form 2016
2017	150 391 000	1 513 385 481	Phase 2, phase 2	Phase 2 started in September 2017	10-k form 2017
2018	199 709 000	513 779 724	Phase 2		10-Q form ended March 31, 2018

EUR, Euro (currency); USD, United States dollars.

Table 6
Current intellectual property or regulatory protection for AVXS-101 (by Novartis AG).

Type of protection	Year of expiration	Country/region
Patent on vector	2024	US
Patent on vector	2024	US
Patent on vector	2026	US
Patent on method of treatment	2028	US
Patent on method of treatment	2028	US
ODE for SMA	2026	US
RDP	2031	US
Patent on vector	2024	EU
Patent on vector	2028	EU
Patent on method of use	2028	EU
Patent on method of use	2028	EU
ODE for SMA	2030	EU
RDP	2030	EU

EU, European Union; ODE, orphan drug exclusivity; RDP, regular data protection; SMA, spinal muscular atrophy; US, United States.

(with Novartis AG), Novartis AG did not report R&D figures for AVXS-101separately. Monthly R&D expenses were calculated by subtracting the expenses recognized pursuant to the REGENXBIO SMA License and the Généthon agreement described above (i.e., a total of 135 200 000 USD) from the total R&D expenses for the first quarter in 2018 (i.e., 199 709 000 USD) and dividing this by three months. Monthly R&D expenses were hence estimated to be 21 503 000 USD (19 061 008 EUR). Adjusted with a success rate of 83.2% (because AVXS-101 was already in its registrational phase and a yearly cost of capital rate of 10.5%, monthly R&D expenses for this period were 23 101 281 EUR). Multiplied by 14 months, a total of 323 417 940 EUR for the time between March 2018 and May 2019 was added.

Appendix C. Number of patent years remaining

Number of patent years left for OTL-200

No reliable figures on IPP could be retrieved for OTL-200. In their SEC filings, ORTX mentioned that they "[...] do not own any patents or patent applications that cover Libmeldy [...]" [36]. Eventual IPP rights seem to be covered by license agreements with GSK. The European Union Register of medicinal products for human use states that the orphan market exclusivity for OTL-200 will expire on 18 December 2030 [37].

Number of patent years left for AVXS-101

The number of patent years left for AVXS-101was extracted from the 2020 20-F form to the SEC by Novartis AG. The reported patents can be fully owned, co-owned or exclusively in-licensed by Novartis AG and relate to at least one dosage strength of AVXS-101, the method of treatment, or its use as it is currently approved and marketed. The reported data on intellectual property or regulatory protection for AVXS-101 are summarized in Table 6. For the base case analysis, we assumed the maximum time for the patent expiration (i.e., the year 2031).

Table 7
Total assumed eligible incident population for OTL-200.

Region	Total eligible patients based on mean	Total eligible patients based on min	Total eligible patients based on max
Europe	378.31	331.02	425.60
Other (more developed)	304.34	266.30	342.39
Total	682.66	597.33	767.99

Appendix D. Estimating incidence and prevalence rates

Metachromatic leukodystrophy (MLD)

MLD incidence rates (or birth prevalence rates) were reported to be between 1.4 and 1.8 per 100 000 [21,40]. For the base-case analysis, we assumed an average incidence rate of 1.6 per 100 000. The assumed incident eligible cases over a period of 10 years are summarized in Table 7.

Spinal muscular atrophy (SMA)

Childhood SMA is categorized into three clinical groups (i.e. type I to type III SMA), based on the age of onset and clinical course [41,42]. While SMA can be classified according to these groups, it should be noted that the disorder demonstrates a continuous range of severity [43]. For this analysis we relied on SMA type specific incidence and prevalence rates summarized in a recent systematic literature review by Verhaart *et al.* [23].

Current marketing approval for AVXS-101 also involves some stratification of the survival motor neuron (SMN) gene. This is because SMA is caused by homozygous disruption of the SMN gene by deletion, conversion or mutation [44]. The SMN gene is present in multiple copies in the human genome: one SMN1 and several SMN2. In more than 98% of patients with SMA, SMN1 is homozygously disrupted by deletion, rearrangement or mutation, whereas at least one copy of SMN2 is typically retained [45,46].

Of those patients, we assumed that all patients with SMA type I or type II would be eligible for AVXS-101in the United States and Japan. For the region of Europe, we used the definition of the EMA approval in which all patients with SMA type I would be eligible and those patients with SMA type II with up to three copies of the SMN2 gene. The proportion of the latter was based in information provided in Calucho *et al.* [22] and was 94.66%.

Type I SMA

Included prevalent patients

Since life expectancy of patients with SMA type I is usually less than the age of two years, we used the total prevalent population with SMA type I to calculate the eligible patient population for the first year of the analysis. The total SMA type I *prevalent* cases for the first year of the analysis that are considered eligible for AVS-101, are summarized in Table 8. This estimate considers that 98% of SMA cases present with a disrupted SMN1 gene and would therefore be eligible for therapy [45,46].

Included incident patients

The total SMA Type I *incident* cases were based on all incident cases as from the first year of the analysis until patent expiration of AVS-101. The base-case assumes a patent expiration after 10 years. Based in this, the number of eligible SMA Type I patients are summarized in Table 9. This estimation accounts for 98% of patients presenting with a disrupted SMN1 gene and includes only patients with up to three copies of the SMN2 gene for the region of Europe.

Table 8
Total prevalent SMA Type I cases in the UN 'more developed' region based in mean, min, and max prevalence rates (PR).

SMA	Based on mean PR	Based on min PR	Based on max PR
Type I	2172	1249	3494

Table 9
Estimated patients with SMA type I eligible for AVXS-101 in 10 years.

Region	SMA Type	Based on mean incidence rate (IR)	Based on min IR	Based on max IR
Europe	I	4013	2503	6812
Other (more developed)	I	3229	2013	5480

Table 10
Total eligible SMA type II cases in 10 years, younger than the age of two years in the UN "more-developed" region based on mean, min and max prevalence rates (PR).

Region	Based on mean PR	Based on min PR	Based on max PR
Europe	370	119	761
Other (more developed)	275	88	566

Table 11
Estimated patients with SMA type II eligible for AVXS-101.

Region	Based on mean IR	Based on min IR	Based on max IR
Europe	1900	592	3487
Other (more developed)	1648	514	3024

Total included SMA type I prevalent and incidence patients were thus 9414 patients, based on the mean reported prevalence and incidence rates over a 10-year period. Based on the minimum and maximum reported prevalence and incidence rates, this were 5765 and 15 786 patients, respectively over a ten-year period.

Type II SMA

Included prevalent patients

Eligible *prevalent* patients for AVXS-101with SMA type II were estimated by calculating the SMA type II prevalent population (taking into account that 98% of the cases present with a disrupted SMN1 gene and only considering those patients with up to three SMN2 copies for the region of Europe) and considering only those 3% that were thought to be below the age of two years. These estimates are presented in Table 10.

Included incident patients

The total eligible *incident* SMA Type II population was based on all incident cases as from the first year of the analysis until patent expiration of AVS-101 (i.e., 10 years). The assumed cases are presented in Table 11.

Total included SMA type I prevalent and incidence patients were thus 4193 patients, based on the mean reported prevalence and

Table 12
Results of the deterministic sensitivity analysis.

Therapy	Model input parameter changed	Value in use	Price in EUR	Absolute difference from base-case price in EUR
OTL-200	Cost of research and development	227 778 464	499 221	−548 917
		290 263 583	609 004	−439 134
		352 748 701	718 788	−329 350
		415 233 820	828 571	−219 567
		477 718 938	938, 355	−109 783
		873 732 926	1 634 133	585 995
		1 207 261 795	2 220 128	1 171 990
		1 540 790 663	2 806 123	1 757 985
		1 874 319 532	3 392 118	2 343 980
		2 207 848 401	3 978 114	2 929 976
	Number of patients	597	1 184 861	136 723
		614	1 154 454	106 316
		631	1 125 703	77 565
		649	1 098 477	50 339
		666	1 072 657	24 519
		700	1 025 088	−23 050
		717	1 003 131	−45 007
		734	982 192	−65 946
		751	962 200	−85 938
		768	943 093	−105 045
	Cost of drug manufacturing	23 033	985 045	−63 093
		31 122	997 664	−50 474
		39 211	1 010 283	−37 855
		47 299	1 022 901	−25 237
		55 388	1 035 520	−12 618
		67 648	1 054 645	6507
		71 819	1 061 152	13 014
		75 991	1 067 659	19 521
		80 162	1 074 166	26 028
		84 333	1 080 673	32 535
	Profit margin	0%	873 448	−174 690
		4%	908 386	−139 752
		8%	943 324	−104 814
		12%	978 262	−69 876
		16%	1 013 200	−34 938
		36%	1 187 890	139 752

(*continued*)

Table 12 (*Continued*)

Therapy	Model input parameter changed	Value in use	Price in EUR	Absolute difference from base-case price in EUR
		52%	1 327 642	279 504
		68%	1 467 393	419 255
		84%	1 607 145	559 007
		100%	1 746 897	698 759
AVXS-101	Cost of research and development	1 624 092 896	242 253	−138 191
		1 937 487 753	269 891	−110 553
		2 250 882 610	297 529	−82 915
		2 564 277 467	325 167	−55 277
		2 877 672 324	352 806	−27 638
		3 344 741 958	393 997	13 553
		3 498 416 734	407 549	27 105
		3 652 091 511	421 102	40 658
		3 805 766 288	434 654	54 210
		3 959 441 065	448 207	67 763
	Number of patients	7077	640 112	259 668
		8383	555 815	175 371
		9689	494 244	113 800
		10 995	447 299	66 855
		12 301	410 322	29 878
		15 611	344 318	−36 126
		17 615	316 412	−64 032
		19 618	294 216	−86 228
		21 622	276 125	−104 319
		23 626	261 103	−119 341
	Cost of drug manufacturing	23 033	317 351	−63 093
		31 122	329 970	−50 474
		39 211	342 588	−37 856
		47 299	355 207	−25 237
		55 388	367 825	−12 619
		67 648	386 951	6507
		71 819	393 458	13 014
		75 991	399 965	19 521
		80,162	406 472	26 028
		84,333	412 979	32 535
	Profit margin	0%	317 037	−63 407
		4%	329 718	−50 726
		8%	342 400	−38 044
		12%	355 081	−25 363
		16%	367 763	−12 681
		36%	431 170	50 726
		52%	481 896	101 452
		68%	532 622	152 178
		84%	583 348	202 904
		100%	634 073	253 629

EUR, Euro (currency).

incidence rates over a 10-year period. Based on the minimum and maximum reported prevalence and incidence rates, this were 1313 and 7838 patients, respectively, over a 10-year period.

In conclusion, the total eligible patient population for AVXS-101for the base-case analysis was 13 607 patients (9414 for type I and 4193 for type II), based on the mean reported incidence and prevalence rates.

Appendix E

For both therapies we had estimated R&D expenses for the base-case analysis. For the deterministic sensitivity and scenario analyses, we sought to increase and decrease these base-case estimates to cover a reasonable range of possible R&D values for each therapy separately. To this end, we based the minimum and maximum R&D values of each therapy on the 0.05 and 0.95 percentiles of a truncated normal distribution, respectively [54].

Due to its symmetrical properties, the normal distribution was suitable because the probability of occurrence of values below and above the assumed mean (in this case the base-case R&D estimates) was sought to be similar [54]. In addition, truncation allowed limiting R&D expenses to positive values [54].

The truncated normal distribution was parametrized as follows. For the mean, we used the base-case R&D estimate of each therapy (i.e., different estimate per therapy).

The standard deviation (SD) was assumed to be equal to the SD of the R&D expense range reported by Schlander *et al.* (i.e., 146 million EUR to 4.11 billion EUR). Since Schlander et al. did not report the SDs for the 45 included unique estimates, we used the improved "range rule of thumb," suggested by Ramirez and Cox [55].

Table 13
Results of the scenario analyses for OTL-200 and AVXS-101.

Scenario number	Price for OTL-200 in 2020 EUR	Price for AVXS-101 in 2020 EUR
1	499 221	242 253
2	3 978 114	448 207
3	1 184 861	640 112
4	943 093	261 103
5	985 045	317 351
6	1 080 673	840 781
7	873 448	317 037
8	1 541 636	559 570

EUR, Euro (currency).

Lower and upper truncation bounds were based on minimum (i.e., 146 million EUR; 161 million USD) and maximum (i.e., 4.11 billion EUR; 4.54 billion USD) R&D values reported in a recent review [25].

Consequently, the SD and lower/upper bounds (informed by the literature) were kept constant, while the mean of the truncated normal distribution was depending on the therapy.

These calculations were done using R version 4.2.1 and the R package truncnorm (Version 1.08).

Appendix F. Results of the deterministic sensitivity analysis

See Table 12

Appendix G. Results of the scenario analyses

See Table 13

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