BMJ Global Health

Ultraexpensive gene therapies, industry interests and the right to health: the case of onasemnogene abeparvovec in Brazil

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To cite: Ivama-Brummell AM, Wagner AK, Pepe VLE, *et al*. Ultraexpensive gene therapies, industry interests and the right to health: the case of onasemnogene abeparvovec in Brazil. *BMJ Global Health* 2022;**7**:e008637. doi:10.1136/bmjgh-2022-008637

Handling editor Seye Abimbola

Received 26 January 2022
Accepted 6 February 2022

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INTRODUCTION

The US Food and Drug Administration (FDA) approval of onasemnogene abeparvovec in 2019 has been a matter of significant controversy. Onasemnogene abeparvovec is a gene therapy indicated for children less than 2 years old with a certain type of spinal muscular atrophy (SMA). Its clinical development benefited from considerable public funding.[1 2] When the medicine received the green light from the FDA, it was hailed as a 'cure' for this debilitating and life-threatening condition. At a list price of US$2 125 000 for a one-time infusion, onasemnogene abeparvovec is the most expensive drug treatment to date.[1] Much has been written about the drug's price, the uncertainties about its efficacy and payer strategies to facilitate access to the treatment for severely ill children in high-income countries.[1]

The dilemmas faced by families, decision-makers and health systems in middle-income countries have received relatively less attention. The ongoing saga of onasemnogene abeparvovec in Brazil illustrates the ever-growing chasm between the promise of medical innovation and affordable access for those who need it, in the context of a complex upper middle-income country health system that also influences health regulation in other Latin American countries.[3]

As the first Latin American regulator to do so, Brazil's Anvisa (Brazilian Health Regulatory Agency) granted marketing authorisation to onasemnogene abeparvovec for the treatment of SMA on 17 August 2020. SMA affects approximately 250–300 newborns in Brazil every year.[4] The approval was based on data that were nearly identical to those for the initial US FDA approval: three single-arm clinical trials involving a total of 48 patients. Following regulatory approval, important uncertainties remained about the long-term safety and clinical effectiveness of the drug.[1]

Summary box

- Onasemnogene abeparvovec—the world's most expensive treatment to date—received Brazilian marketing authorisation for the treatment of spinal muscular atrophy in August 2020.
- In the absence of convincing evidence supporting the drug's added therapeutic benefit over existing alternatives, the Brazilian drug pricing authority later approved a maximum price that was 77% lower than the manufacturer's intended price.
- In response, the drug's manufacturer decided not to commercialise onasemnogene abeparvovec in Brazil.
- Yet, courts have obliged the Ministry of Health to fund the treatment citing the right to health legislation, at prices that are more than three times higher than the maximum approved price in the country.
- The case of onasemnogene abeparvovec in Brazil highlights the ever-growing chasm between the promise of medical innovation and affordable access for those who need it in resource-constrained health systems.

According to the latest results of an ongoing single-arm study, the therapy does not appear to be as effective as initially thought.[1 5]

In the absence of convincing evidence supporting the treatment's added therapeutic benefit over existing alternatives, the Brazilian drug pricing authority [Drug Market Regulation Chamber (CMED)] approved in December 2020 a maximum provisional price that was 77% lower than the manufacturer's intended price (BRL2.9 million; US$531 173.2; £396 516.4).[6] Brazil was not alone in recommending such substantial price reductions for onasemnogene abeparvovec, as health authorities in several high-income countries, based on limitations in clinical evidence, recommended price reductions that ranged from 50% to 90% of the manufacturer's asking price (table 1).

Table 1 Appraisal of onasemnogene abeparvovec and recommendations from different health authorities

Country	Canada	France	Germany	The Netherlands	England
Authority	CADTH Canadian Drug Expert Committee (CDEC) (published on 26 March 2021)	*Haute Autorité de Santé* (HAS) [French National Authority for Health] (published on 16 December 2020)	*Gemeinsamer Bundesausschuss* (G-BA) [Federal Joint Committee] (published on 20 January 2022)	*Zorginstituut Nederland* (ZIN) [The National Health Care Institute] (published on 4 April 2021)	National Institute for Health and Care Excellence (NICE) (published on 7 July 2021)
Indication	Treatment of paediatric patients with 5q spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (SMN1) gene and three or fewer copies of SMN2 gene, or infantile-onset SMA.	Patients with 5q SMA with a biallelic mutation of the SMN1 gene and having a clinical diagnosis of SMA type 1, or patients with 5q SMA with a biallelic mutation of the gene SMN1 and up to three copies of the SMN2 gene.	Patients with 5q-associated SMA with a biallelic mutation in SMN1 gene and one clinically diagnosed SMA type 1, or up to three copies of the SMN2 gene.	Patients with SMA: ▶ All symptomatic patients with SMA type 1. ▶ Presymptomatic patients with SMA with up to three copies of the SMN2 gene.	Expected to be indicated for the single treatment of 5q13 SMA type 1.
Paediatric population	Health Canada (≥8 months of age): the efficacy and safety of onasemnogene abeparvovec in paediatric patients 8 months of age and older at the time of infusion have not been established in clinical trials.	EMA: there is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established.	EMA: there is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established.	EMA: there is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established.	MHRA: there is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established.
Recommendation	Conditional recommendation to be reimbursed for the treatment of paediatric patients with 5q SMA with biallelic mutations in the SMN1 gene. Conditioned to initiation criteria, prescribing conditions and price reduction.	Reimbursement for the treatment of patients with 5q SMA (biallelic mutation of the SMN1 gene), with a clinical diagnosis of SMA type 1 and type 2 or presymptomatic, with up to three copies of the SMN2 gene.	No added benefit of onasemnogene abeparvovec has been proven for any type of SMA.	Cost-effectiveness is unfavourable and very uncertain. Conditional recommendation to be included in the insured package with price reduction, pay for performance and joint price negotiation with Belgium and Ireland.	Recommended to be offered at the NHS under managed access agreement, including additional data collection.

Continued

Table 1 Continued

Country	Canada	France	Germany	The Netherlands	England
Limitations	Major limitations are the lack of a concurrent control group that precludes a precise estimation of the magnitude of benefit and lack of information on the long-term comparative clinical effectiveness of onasemnogene abeparvovec versus comparators.	Uncertainties of long-term effect and significant limitation related to the absence of a robust direct or indirect comparison with nusinersen, which does not make it possible to know exactly the place of onasemnogene abeparvovec in the therapeutic strategy of patients with SMA type 1.	No direct comparison studies were available. In addition, different exclusion criteria and study populations (age, severity of disease) in the different studies make comparisons difficult. No suitable data were available for three of the four research questions.	Uncertainties about the long-term effects and the use of additional treatments (such as nusinersen).	Small sample sizes in all clinical trials; naïve comparison of the indirect comparison with nusinersen does not preserve within-study randomisation or consider differences in study effects, all results should be interpreted with caution.
Recommended price reduction	More than 90%.	Recommend an agreement with additional data collection.	Collection of further evidence.	At least 50%, pay for performance.	Managed access agreement with further data collection.
Sources	CADTH: https://cadth.ca/sites/default/files/cdr/complete/SG0649 Zolgensma - CDEC Final Recommendation March 26%2C 2021 for posting.pdf (accessed on 20 January 2022)	HAS: https://www.has-sante.fr/upload/docs/application/pdf/2021-11/zolgensma_161220_summary_ct18743.pdf(accessed on 20 January 2022)	G-BA: https://www.g-ba.de/beschluesse/5246/ (accessed on 25 January 2022)	Zin: https://www.zorginstituutnederland.nl/over-ons/publicaties/adviezen/2021/04/23/acp-advies-over-onasemnogene-abeparvovec-zolgensma (accessed on 20 January 2022)	NICE: https://www.nice.org.uk/guidance/hst15/evidence/evaluation-consultation-committee-papers-pdf-9191287693 (accessed on 20 January 2022)

CADTH, Canadian Agency for Drugs and Technologies in Health (Canada); EMA, European Medicines Agency (Europe); MHRA, Medicines and Health Products Regulatory Agency (UK); NHS, National Health Service; SMA, spinal muscular atrophy ; SMN, survival motor neuron.

Box 1 Litigation or 'judicialization' and the right to health in the Brazilian Unified Health System

In Brazil, the right to health is a constitutional right. The Brazilian Unified Health System (*Sistema Único de Saúde*, known as SUS) is a universal national health system, free at the point of care. It is decentralised; the federal level, states and municipalities share its governance and funding through tax revenue and social contributions. Health expenditure corresponded to 9.1% of gross domestic product (GDP) in 2015, with public spending accounting for 42.8%, and 75% of Brazilians relying solely on SUS. About 5% of families, disproportionally poor, incur catastrophic out-of-pocket expenditures due to the cost of certain medicines not covered free of charge by SUS.

Marketing authorisation by the Brazilian Health Regulatory Agency (Anvisa) and maximum price approval by the Drug Market Regulation Chamber (CMED) are mandatory for medicines to reach the Brazilian market. CMED is responsible for the economic regulation of the pharmaceutical market for promoting sustainable access to medicines. All authorised prices are publicly available. Medicines and other health technologies need to be assessed by the National Commission for the Incorporation of Technologies in the SUS (Conitec) and approved by the Ministry of Health to be provided by the SUS.[11]

Health litigation or *judicialisation* occurs in many countries where a 'right to health' legal framework clashes with limited government resources and is very common in Brazil, Colombia and South Africa. Lawsuits can contribute to increasing inequalities by forcing the allocation of resources for unplanned expenses under an already constrained budget, posing an ethical dilemma for the payer.[12] Patient advocacy groups and law firms, often financed by pharmaceutical companies, support families in the process of suing for government coverage of a therapy, specifically a highly priced medicine.[13]

In several court cases, medicines were provided even before marketing authorisation and price approval, at much higher prices than authorised by CMED.[13] Judges have been found to rule frequently in favour of patients and their families. In addition, patients can apply for anticipated or urgent relief measures, even before the court decision is issued.

Costs of lawsuits increased from 8% in 2012 to 22% of the public pharmaceutical expenditure on specialty medicines in 2018, of which 20 medicines were responsible for 95% of the expenditures following lawsuits, 60% of them without marketing authorisation and none of them approved to be covered by the SUS.[14] Exceptions for SUS coverage of medicines not yet approved should be based on recommendations by the National Council of Justice (CNJ). In 2015, the Technical Support Centres of the Judiciary Power (NATJUS) and its repository of technical documents (e-NATJUS) were created to provide evidence-based support for the State Courts of Justice and the Federal Regional Courts' decision-making in litigation cases related to health. In addition, the High Court established parameters for judicial decisions, the thesis of general repercussion, and the CNJ established consensus (*enunciados*) to guide future lawsuit decisions. In 2020, the CNJ stated that the SUS should not provide medicines without proven efficacy, safety and marketing authorisation by Anvisa. The challenge is to make sure the court decisions are aligned with these recommendations.

Nevertheless, in March 2021, after the rejection of its first appeal of the pricing decision, the drug's manufacturer, Novartis, issued a public statement arguing that the authorised price was commercially unviable 'in view of the research and development, production, logistics and distribution costs'. The manufacturer later appealed to the CMED Minister's council and decided not to commercialise the treatment in Brazil, urging the authorities to consider the innovative value of the therapy.[7] As of January 2022, the case had not yet been resolved. The medicine therefore remains unavailable in Brazil—at least officially.

RIGHT TO HEALTH

While the regulatory assessment of the treatment was underway, families of children with SMA sued the government for immediate access to onasemnogene abeparvovec on the grounds of the right to health legislation. The courts have obliged the Ministry of Health to provide families of patients with the resources to import the therapy at prices considerably higher than those ultimately approved in the country (box 1).

The court cases have been accompanied by an intensely politicised and concerted media campaign with celebrities advocating for the regulatory approval and reimbursement of the drug. Import tax for the therapy was waived ahead of marketing authorisation, and two bills currently in the Brazilian Congress propose the mandatory provision of onasemnogene abeparvovec by the Ministry of Health without any health technology assessment, even though the latter is a legally mandated step for any medicine or technology to be incorporated into the Brazilian Unified Health System.[8]

By October 2021, court decisions had forced the Ministry of Health to fund the treatment of 46 patients with onasemnogene abeparvovec, at a total cost of US$79 million (£58.9 million). The average cost of the drug (US$1.7 million, £1.3 million) per patient is more than triple the maximum approved price by the Brazilian CMED. Lawsuits against states and private health insurance plans resulted in additional mandates for payment, including children older than 2 years for whom the therapy is not indicated in Brazil.

The court-mandated provision of onasemnogene abeparvovec comes with high opportunity costs, as the Ministry is obliged to provide the resources for patients to import the drug at unregulated prices. The resources spent by the Ministry of Health on the treatment of 46 patients would have been more than sufficient to treat all babies born with SMA type 1 in Brazil in a year (189 patients) at the approved maximum government procurement price. At least US$60 million (£44.6 million) (75% of the expenditures on the therapy) could have been saved if their treatments were purchased at the approved maximum government procurement price. The lawsuit expenses correspond to 3.8% of the Ministry of Health's entire pharmaceutical expenditures in 2020, enough to treat 5805 patients with specialty drugs (10.3% of the expenditure on specialty medicines) in the

same year or to procure 4.3 million doses of the COVID-19 vaccine.[9]

WHAT IS AT STAKE?

Brazil has a universal health system with regulatory, pricing and reimbursement frameworks carefully designed to provide access to medicines to its population while stewarding limited resources. CMED's mandate is to ensure that prices are commensurate with drug benefits within the constraints of affordability. The manufacturer of onasemnogene abeparvovec did not comply with the Brazilian regulator's pricing decision. Instead, the drug's manufacturer benefited from a combination of judicial routes, efforts to change the legislation and an extensive media presence—all conducted through proxies—to promote a narrative that pricing policies are responsible for restricting patient access to innovative medicines. This case shows how a country's regulatory and pricing system can be rendered ineffective and indeed the entire health system threatened when powerful multinational pharmaceutical companies do not respect its underlying principles and the legal system inadvertently facilitates an industry strategy that exploits the vulnerabilities of the country's governance.

CONCLUSION

The right to health is an important achievement in Brazil. It is necessary to ensure access to appropriate care for those who need it. Exploitation of that right through judicialisation of onasemnogene abeparvovec access has placed on the society the burden of funding the provision of an extremely expensive medicine with high opportunity costs. Efforts are needed to minimise the impacts of current and avoid future lawsuits, and to enforce the application of the existing regulatory, pricing and coverage regulations to prevent provision of new medicines without robust evidence at excessively high prices and enormous societal cost.

The unfolding saga of onasemnogene abeparvovec reminds us that the regulation and pricing of medicines is at the intersection of societal values, science, medical culture, patient needs and expectations, economics and politics.[10] We therefore suggest that corporate social responsibility, market approval, pricing and reimbursement policies be considered in a broader, societal context.

Contributors AMIB and HN had substantial contributions to the conception of the work. AMIB was responsible for drafting the work and data acquisition. All authors had substantial contributions to the analysis and interpretation of the data, revised critically and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The views expressed in this commentary do not necessarily reflect those of the Brazilian Health Regulatory Agency (Anvisa) or the Executive Secretariat of the Drug Market Regulation Chamber (SCMED).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The information on pharmaceutical expenditure and prices is publicly available. The expenditure and number of patients receiving onasemnogene abeparvovec were provided by the Ministry of Health under the provisions of the Brazilian Law of Access of Information (LAI). Novartis later removed the original statement issued on March 8th 2021 (https://www.novartis.com.br/news/atualizacao-sobre-o-preco-de-zolgensma) from their website. A copy of the original statement is available from the first author upon request.

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