Journal of Cystic Fibrosis 21 (2022) 866–872

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Current prices versus minimum costs of production for CFTR modulators

Jonathan Guo[a,*], Junzheng Wang[a], Jingchun Zhang[b], Joseph Fortunak[c], Andrew Hill[d]

[a] School of Public Health, Faculty of Medicine, Imperial College London, United Kingdom
[b] Department of Biomedical Engineering, University of North Dakota, United States of America
[c] Chemistry and Pharmaceutical Sciences, Howard University, United States of America
[d] Department of Pharmacology and Therapeutics, University of Liverpool, United Kingdom

ARTICLE INFO

Article history:
Received 29 December 2021
Revised 21 March 2022
Accepted 1 April 2022
Available online 16 April 2022

Keywords:
Cystic fibrosis
Cystic fibrosis transmembrane conductance regulator
Trikafta
Kaftrio
CFTR modulator
Elexacaftor/tezacaftor/ivacaftor

ABSTRACT

Background: While the clinical benefits of CFTR modulators are clear, their high prices render them inaccessible outside of the world's richest countries. Despite this, there is currently limited evidence regarding global access to these transformative therapies. Therefore, this study aims to estimate the minimum costs of production of CFTR modulators, assuming robust generic competition, and to compare them with current list prices to evaluate the feasibility of increased global access to treatment.

Methods: Minimum costs of production for CFTR modulators were estimated via an algorithm validated in previous literature and identification of cost-limiting key starting materials from published routes of chemical synthesis. This algorithm utilised per kilogram active pharmaceutical ingredient costs obtained from global import/export data. Estimated production costs were compared with published list prices in a range of countries.

Results: Costs of production for elexacaftor/tezacaftor/ivacaftor are estimated at $5,676 [$4,628-6,723] per year, over 90% lower than the US list price. Analysis of chemical structure and published synthetic pathways for elexacaftor/tezacaftor/ivacaftor revealed relatively straightforward routes of synthesis related to currently available products. Total cost of triple therapy for all eligible diagnosed CF patients worldwide would be $489 million per year. Comparatively, the annual cost at US list price would be $31.2 billion.

Conclusions: Elexacaftor/tezacaftor/ivacaftor could be produced via generic companies for a fraction of the list price. The current pricing model restricts access to the best available therapy, thereby exacerbating existing inequalities in CF care. Urgent action is needed to increase the availability of triple combination treatment worldwide. One strategy based on previous success is originator-issued voluntary licenses.

© 2022 The Author(s). Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

1. Introduction

In recent years, management for cystic fibrosis (CF) has advanced drastically, culminating in the development of CFTR modulators able to target the root cause of the condition. Four such drugs are currently licensed and sold by Vertex Pharmaceuticals: ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor. The most recent of these – the triple combination elexacaftor/tezacaftor/ivacaftor – is suitable for the largest proportion of mutation profiles (an estimated 90% of all CF patients) [1] and shows significantly improved outcomes when compared with both placebo and previous generation therapies [2].

These drugs currently represent the best available treatment for CF, and an opportunity to improve quality and length of life for almost all patients, yet US list prices for CFTR modulators are over $250,000 per year [3]. This pricing strategy represents a huge barrier to effective and equitable treatment, with worldwide estimates of the proportion of CF patients receiving elexacaftor/tezacaftor/ivacaftor as low as 12% [4]. In addition, it renders the medicines out of reach for patients unless reimbursed by government or health system authorities. Even still, CFTR modulators pose resource allocation dilemmas to even the most robust and well-funded of health systems. This was demonstrated recently in negotiations between Vertex and NHS England regarding prices for lumacaftor/ivacaftor, which lasted four years and culminated in the destruction of 7,880 packs of expired drug [5]. Such protracted negotiations occur at the cost of patients, who remain in limbo un-

* Corresponding author.
E-mail address: jyg17@ic.ac.uk (J. Guo).

https://doi.org/10.1016/j.jcf.2022.04.007
1569-1993/© 2022 The Author(s). Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

able to obtain life-changing treatments, causing some to even resort to setting up "buyers clubs" to bypass both Vertex and regulatory bodies [6].

The benefits of CFTR modulator therapy are so profound that delays in access cause very tangible impacts on patient outcomes. For example, Stanojevic and colleagues demonstrated that universal introduction of elexacaftor/tezacaftor/ivacaftor in 2021 would reduce the number of people living with severe lung disease by 60% and deaths by 15% by 2030, with these benefits halved if introduction was delayed to 2025 [7].

Although much of the current documented CF burden lies in high-income countries (HICs), recent research suggests a high level of underreporting of CF in low- and middle-income countries (LMICs), due to ascertainment bias and lack of patient registries [1,8]. While the current pricing model delays access to treatment in HICs, it entirely disregards patients and health systems in LMICs where poorer CF outcomes are already experienced [1], thereby creating a two-tiered standard of care. Currently CFTR modulators are almost exclusively available in the world's richest countries – as of June 2021, elexacaftor/tezacaftor/ivacaftor was only reimbursed in 16 countries worldwide. Despite this, little evidence currently exists on worldwide access to CFTR modulators.

Similar challenges in treatment access have been overcome for other conditions. In the case of triple combination antiretroviral (ARV) therapy used for the treatment of human immunodeficiency virus, as well as direct-acting antivirals (DAAs) for treatment of hepatitis C, similarly prohibitive drug prices were reduced by over 90% [9]. This was achieved via generic competition introduced through use of voluntary licensing, with subsequent increased volume demand and production efficiency [9,10], and allowed millions in resource-limited settings access to lifesaving drugs.

Such price decreases were deemed ambitious and infeasible at the time and yet have resulted in significantly improved treatment uptake and patient outcomes [11]. As such, using the precedents set by these pharmaceutical agents, this study aims to provide novel estimates of the minimum costs of production of CFTR modulators, assuming robust generic competition, and to compare them with current list prices to evaluate the feasibility of increased global access to treatment.

2. Methods

2.1. Minimum costs of production

Methodologies utilising prices of active pharmaceutical ingredient (API) have been described in previous research to reliably estimate minimum costs of production for standard oral formulations [10,12,13]. Since all CFTR modulator therapies on the market are taken PO, an algorithm adapted from Hill et al. was used to estimate costs of production. All four CFTR modulators with FDA and EMA approval were included within this study, though our analysis focused on lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor due to their increased efficacy and patient eligibility when compared with ivacaftor monotherapy [1].

Generic production in India (or China) was assumed as these are the world's leading producers of both generic medications and API [14]. The import/export databases Panjiva and SINOIMEX, alongside PharmaCompass were used to analyse all available cost data for shipments of relevant API from 1st January 2016 to July 2021 [15–17]. Shipments containing less than 1kg of API or API in combination with another product were excluded to avoid analysis of shipments of completed drug or samples not intended for large-scale production. Duplicates were removed and shipments with a price per kilogram outside of the 15th and 85th percentiles excluded to reduce the effect of outliers on our estimates. After completion of our analysis, we included the data outside the 15th and 85th percentiles to assure that these exclusions did not bias results due to any unusual circumstances.

Weighted-mean price per kilogram of API was calculated and combined with dosage information extracted from the British National Formulary (BNF). This was used to calculate API costs for a one-year course of treatment, including an assumed 5% API loss during production. Total production cost was calculated by incorporating costs of excipients (substances required for formulation such as stabilisers, binding agents, disintegration/dissolution enhancers, and coatings) and formulation into a tablet for oral consumption. Previous research has estimated average pharmaceutical excipient cost to be $2.63 per kilogram of finished pharmaceutical product (FPP) [18]. Similarly, per-unit formulation cost was estimated at $0.01 per tablet [12,19]. Finally, a profit margin of 10% was added, as well as an average Indian tax of 27% to calculate FPP price [20].

No API data was available for elexacaftor, likely owing to its novelty. Consequently, for this API estimates of per kilogram costs were made via published routes of chemical synthesis extracted from patent information [21]. Similar analyses were performed based upon chemical structure and synthetic routes for other APIs to identify cost-limiting key starting materials (KSMs) and ensure estimated costs of production were reasonable (these can be found in Appendix 1).

2.2. Sensitivity Analysis

In order to describe the uncertainty associated with the estimates produced by this model approximate 95% confidence intervals were generated for the weighted-mean price per kilogram of each API. This was not possible for tezacaftor due to a lack of available data, and for elexacaftor a margin of error of ±$10,000/kg was included. For each combination treatment, respective values were combined to generate upper and lower bounds to our estimates of minimum costs of production.

2.3. Current list prices

National pricing databases in a variety of countries were searched in August 2021 to provide a snapshot of current publicly available information on list prices, calculated for one-year treatment courses. These were then compared with our estimated minimum costs of production. As it currently represents the largest market for CFTR modulators, for the US, both commercially available price to the public, and costs to the publicly funded veteran's affairs system were listed. Costs from the UK's CF Buyers Club, which enables patients to buy low-cost generic CFTR medications produced in Argentina, are also quoted for completeness. The full list of data sources by country are detailed in Appendix 2.

Where official databases were unavailable, online pharmacy sites were used as an alternative. Where several prices were available in the same database, the lowest was selected. Differences in medicine composition were accounted for between regulatory jurisdictions, with standardisation of pricing based on the dosage regimen found in the BNF.

3. Results

3.1. Minimum costs of production

Weighted-mean API prices for ivacaftor, lumacaftor and tezacaftor were found to be $13,196/kg, $19,673/kg and $51,500/kg respectively. Overall, this study identified shipment volumes of 186.93kg in total for ivacaftor, with 125.96kg being in the latest 12-month period. This was an increase of 314.48% compared to the average annual volume of 30.39kg since 2016. In terms of lumacaftor,

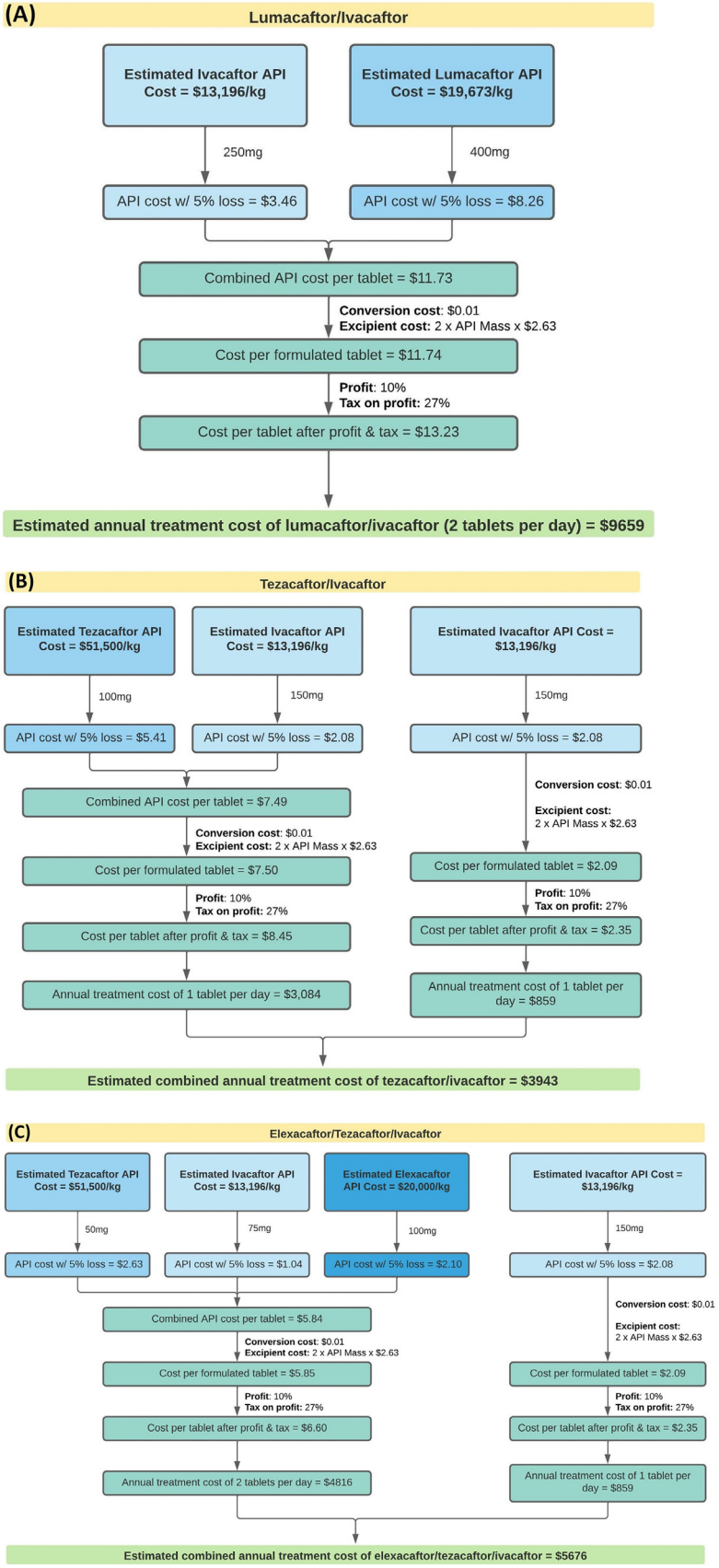

Fig. 1. (A) Flowchart showing minimum cost estimations for lumacaftor/ivacaftor. (B) Flow chart showing minimum cost estimations for tezacaftor/ivacaftor. (C) Flowchart showing minimum cost estimations for elexacaftor/tezacaftor/ivacaftor.

total shipment volumes of 37.76kg were identified, with 16.71kg in the last 12 months and the average annual volume was found to be 5.21kg since 2016. It should be noted that after data cleaning only one shipment result was available for tezacaftor which influences the reliability of this estimate.

Ivacaftor API was shipped from India to the US in 2015 (40 kg) at an average cost of $30,889/kg [22]. This likely represents shipments of API to Vertex in the earlier stages of commercialization. Eight companies (seven in India) have Drug Master Files (DMFs) on this drug with the USFDA [23]. Seven of these companies are Indian; six of them appear capable of making the API while one company (Vindhya) seems to be supplying key starting materials for API production. Eight additional companies advertise their ability to supply the API (without a US or European registration) on the website PharmaCompass. The largest importer of API is Argentina, at an average cost of $12,700/kg.

There is only a single Drug Master File listed for lumacaftor with two API suppliers listed on PharmaCompass. Tezacaftor also has only one listed DMF with the FDA, with three companies listed on PharmaCompass as suppliers of the API. No reliable pricing data is available for these APIs in PharmaCompass.

Analysis of chemical structure and published synthetic pathways for elexacaftor revealed relatively straightforward routes of synthesis. The API is made, however, by putting together multiple modular pieces (starting materials) that are fairly expensive because they are not in high demand for other uses in the chemical industries. Consequently, API cost was estimated to be $20,000/kg. All schema and chemical structures for relevant APIs and KSMs can be found in Appendices 3-7.

3.1.1. Lumacaftor/Ivacaftor

The treatment regimen for lumacaftor/ivacaftor is one 400/250mg tablet taken twice daily. Thus, for a one-year treatment course of lumacaftor/ivacaftor total API cost was $8,153 (Fig. 1a). With incorporation of production costs, the total estimated cost of production for one year of treatment was $9,659. Our model renders lumacaftor/ivacaftor the most expensive of the CFTR modulators to produce. This is likely due to the relatively high daily dosage of API contained within the treatment. Following sensitivity analysis, the highest estimated cost was $10,001, and the lowest $9,317.

3.1.2. Tezacaftor/Ivacaftor

Daily treatment with tezacaftor/ivacaftor entails one 100/150mg tablet followed by one 150mg tablet of ivacaftor. Therefore, estimated total API cost for one year of treatment was $3,325, with a final annual treatment cost of $3,943 after accounting for extra costs of production (Fig. 1b). After sensitivity analysis, the highest estimated cost was $4,127, and the lowest $3,760.

3.1.3. Elexacaftor/Tezacaftor/Ivacaftor

Daily treatment with elexacaftor/tezacaftor/ivacaftor consists of two 100/50/75mg tablets followed by one 150mg tablet of ivacaftor. As such, estimated total API cost for one year of treatment was $4,785. After accounting for production costs, the final estimated annual cost of treatment was $5,676 (Fig. 1c). After incorporating uncertainty, the highest estimated cost was $6,723, with the lowest at $4,628.

3.2. Current list prices for CFTR modulators

Our results are summarised in Table 1 and Fig. 2a-c. Overall, available data was limited to countries where CFTR medications had been approved, which tended to be in western HICs with a relatively high burden of diagnosed disease, and where healthcare systems have the resources available to afford such drugs.

For each combination treatment the highest international price found was via commercial US pharmacy, and the lowest in Argentina. This is likely because in Argentina CFTR modulators are currently not under patent protection, and as such generic versions are available. In all cases commercial prices around the world were many times higher than the costs estimated by our model.

4. Discussion

This novel analysis demonstrates that costs of production for CFTR modulators could be significantly lower than current list prices. Specifically, for the current best available therapy (elexacaftor/tezacaftor/ivacaftor), the lowest originator cost for one year of treatment was $255,600, while the highest production cost estimated by this analysis was $6,723, representing a decrease of over 90%.

Generic versions of all CFTR modulator therapies are produced in Argentina, where patent restrictions currently do not apply. Under the Trade-Related Aspects of Intellectual Property Rights agreement commercial export of generic drugs to a country where such products remain under patent protection is not permitted [24]. As such in this rather unique case the market for generic CFTR modulators is mostly limited to domestic Argentinian CF patients, and there is an absence of the competition usually required to drive down drug prices [9]. Yet even with a limited volume demand and the absence of competition, these generics formed the lowest list price for every modulator combination and can be purchased for prices of ~$15,000 [6,25], indicating the commercial viability of lower cost CFTR modulators and the validity of the minimum prices reached by this analysis.

Several limitations should be noted. Firstly, our model does not account for potentially required investment in new facilities, regulatory approval or costs of research and development (R&D) of products. It also assumes generic production in specific geographical locations with robust mechanisms of competition and sufficient volume demand. Additionally, in previous analyses utilising similar methodologies higher volumes of API were identified. This is likely due to both the novelty and limited manufacture of this class of drugs while they remain under patent, and limits the accuracy of our estimates. However, larger scale production of both API and FPP generally sees prices fall rather than rise due to increased volume demand, process optimisation and production efficiencies [10]. And so smaller shipment volumes would likely produce a higher, rather than lower minimum estimated cost.

Another limitation of note is that actual prices paid for CFTR modulator therapy are likely lower than “list price” following negotiations with payors. While such data is not publicly available, previous research has found discounts for pharmaceuticals tend to range from 20-29% [26], which still places the final prices identified by our survey significantly higher than even the upper bound estimates generated by our analysis. As such even if, for example, a significantly higher profit margin were incorporated into the model to incentivise market entry for generic competitors, the final cost would remain a fraction of contemporary prices.

Furthermore, the model used has been previously validated against 148 drugs on the WHO essential medicines list. As part of this analysis estimated minimum costs were compared with commercial prices for both originator products and generic equivalents produced in India, with prices of generics a median 40% lower than the estimated minimum costs [12]. This model was also applied to DAAs shortly after their discovery, with minimum costs estimated at $100-350 per 12-week course [10,13]. Following voluntary licensing, generic versions of these treatments are now available for under $100 in a variety of jurisdictions, having fallen from launch prices of over $80,000 [27].

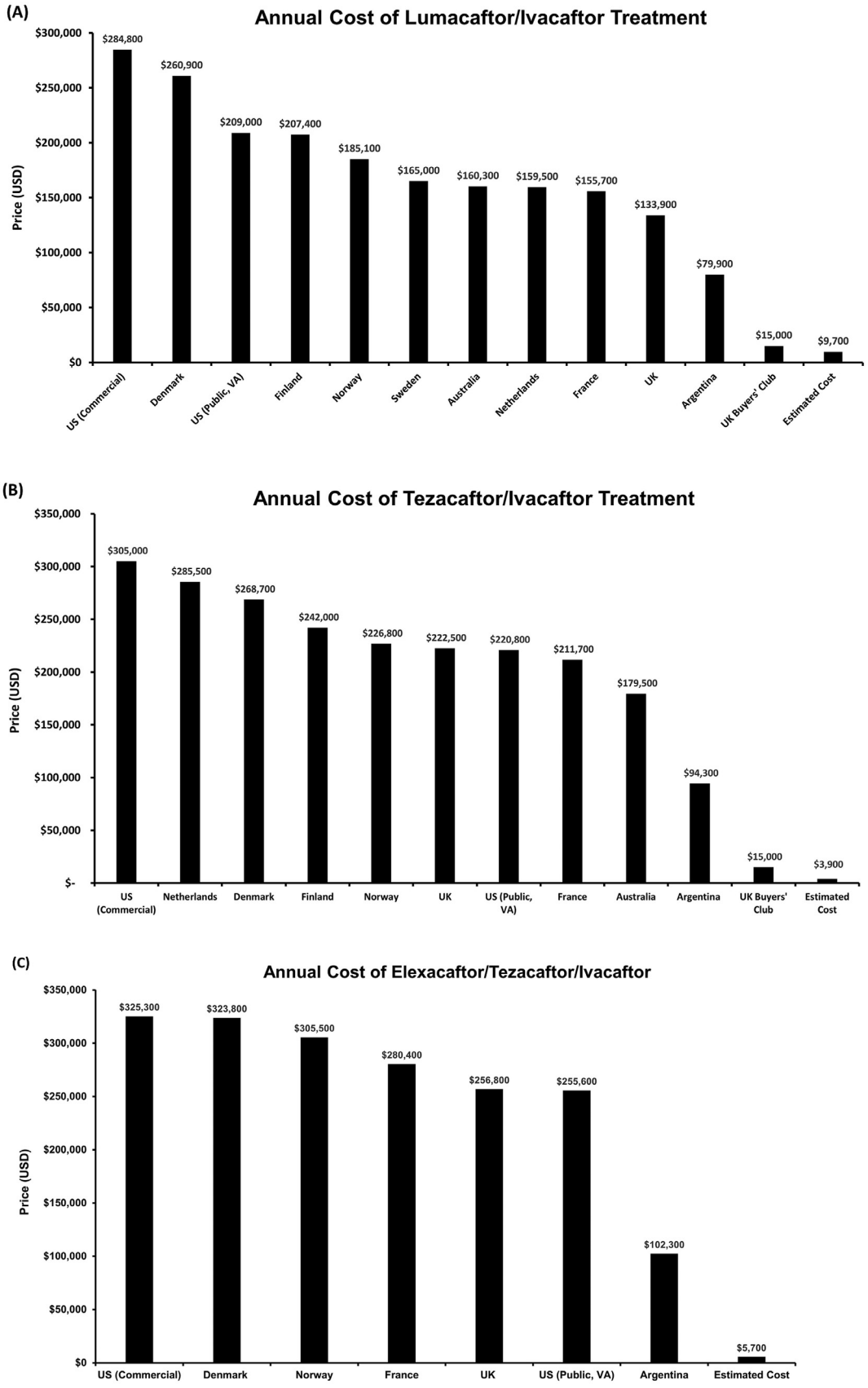

Fig. 2. (A) Graph of national treatment course prices of lumacaftor/ivacaftor compared to generic estimate. (B) Graph of national treatment course prices of tezacaftor/ivacaftor compared to generic estimate. (C) Graph of national treatment course prices of elexacaftor/tezacaftor/ivacaftor compared to generic estimate.

Table 1
Summary of list prices vs estimated production costs for combination CFTR therapies. Costs rounded to nearest $100.

Drug, Duration and Dose	Highest List Price (per annum)	Lowest List Price (per annum)	Estimated Production Cost (per annum)
PO lumacaftor/ivacaftor 400/250mg PO BD	$284,800 US (Commercial)	$79,900 Argentina $15,000 UK CF Buyers Club	$9,700
PO tezacaftor/ivacaftor 100/150mg OD + ivacaftor 150mg OD	$305,000 US (Commercial)	$94,300 Argentina $15,000 UK CF Buyers Club	$3,900
PO elexacaftor/tezacaftor/ivacaftor 200/100/150mg OD + ivacaftor 150mg OD	$325,300 US (Commercial)	$102,300 Argentina	$5,700

OD = once daily, BD = twice daily, PO = by mouth.

As such, while these limitations hinder the ability of our analysis to generate accurate and precise future prices of these drugs, we believe the methodology utilised to be reliable in estimating minimum costs of production from contemporary data and that our results still indicate the economic feasibility of markedly lower prices and wider access for CFTR modulators.

The primary justification for the high prices of CFTR modulators are the costs of R&D. These costs need to be recouped but income is also required to fund research into novel treatments, and for a rare disease such as CF the market is smaller than for other therapeutic areas. However, even with the current limited rollout of elexacaftor/tezacaftor/ivacaftor, it is estimated to be one of the most valuable orphan drugs currently available [28], with quarterly revenues reaching $1.5 billion, exceeding mean estimated costs of bringing a new drug to market [29,30]. Cost-effectiveness analyses by both governmental and independent bodies have concluded that the benefits of CFTR modulators do not warrant their prices [3,31]. It therefore appears prices are not determined via production expenses, R&D costs or efficacy, but rather what the market will bear.

At the time of writing, the total number of CF patients documented in publicly-reporting registries amounted to 95,835 [4]. Assuming this volume demand and a patient eligibility of 90% [1], the annual cost of triple therapy for all eligible patients at the US list price would amount to $31.2 billion [3]. Even assuming negotiated discounts, such a cost represents an enormous barrier to equitable access to treatment, especially given that this estimate is mainly limited to HICs. Comparatively, at the calculated minimum costs of production this could be achieved for $489 million.

It should also be noted that in many LMICs F508del – the mutation targeted by elexacaftor/tezacaftor/ivacaftor – is reported to be a less prevalent disease-causing mutation than in HICs [1]. Consequently, in these regions the benefits of elexacaftor/tezacaftor/ivacaftor may be reduced. However, while less dominant than in HICs, F508del remains a highly significant mutation, and elexacaftor/tezacaftor/ivacaftor has shown efficacy in many rarer non-F508del mutations [32]. Furthermore, as a class of treatments CFTR modulators remain the best available single therapy for CF, and therefore the most appropriate target for improving access.

Patent protection for elexacaftor/tezacaftor/ivacaftor is expected to last until 2037 [3]. Consequently, the current monopoly on modulator treatment is not set to change. It seems there is no transparent plan to increase access to these transformative therapies, as Vertex have largely not sought regulatory approval for modulator therapies outside of the Global North, despite the known disease burden of CF in many countries outside of this region [1]. Outcomes in CF have long been associated with disparities based upon socioeconomic status, both within and between countries of all levels of economic development [33]. As such unless steps are taken urgently to address the prohibitively high prices of CFTR modulators, they will certainly perpetuate and likely exacerbate existing disparities for patients in both LMICs and HICs.

Currently compassionate treatment programs are run by Vertex to provide treatments at lower cost [34]. However, the scale of the issue demands as a solution not philanthropy, but solidarity with stakeholders to provide meaningful action at a country, rather than an individual level [36]. Given our results and that generic commercialisation of CFTR modulators has already been shown to be feasible in Argentina, one key mechanism used to increase access to ARVs and DAAs which could be applied to CFTR modulators is voluntary licensing. Aside from the policy's previous success with other drugs, this strategy is preferable to such price reductions or donation programs as it generates a market for generic competition, thereby providing long-term, sustainable price decreases [35].

5. Conclusion

CFTR modulators could be produced via generic companies for a fraction of current list prices. Country-level reimbursement of modulator therapies fall far short of global disease burden. This is driven by their prohibitively high prices and has led to patients being neglected from advancements in care while exacerbating international disparities in CF outcomes. As such, urgent action to increase the availability of treatment is needed to prevent a widening of existing inequalities. One strategy based on previous success is originator-issued voluntary licenses.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing statement

All data used in this study will be available from the corresponding author, upon reasonable request.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Jonathan Guo: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Junzheng Wang:** Formal analysis, Visualization,

Writing – review & editing. **Jingchun Zhang:** Data curation, Writing – review & editing. **Joseph Fortunak:** Data curation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Andrew Hill:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Acknowledgements

The authors would like to acknowledge the kind support of Rob Long, Gayle Pledger, Christina Walker, George Henning and Susannah Wang.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcf.2022.04.007.

References

[1] Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med 2020;8:65–124. doi:10.1016/S2213-2600(19)30337-6.
[2] Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, et al. VX-445–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. N Engl J Med 2018;379:1612–20. doi:10.1056/NEJMoa1807120.
[3] Seidner M. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Final Evidence Report and Meeting Summary. 2020.
[4] Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. J Cyst Fibros 2022;0. doi:10.1016/j.jcf.2022.01.009.
[5] Wollaston SM, Wollaston D. Written evidence from Vertex Re: Availability of Orkambi on the NHS-Orkambi inventory reserves. 2019.
[6] FAQs — CF Buyers Club n.d. https://www.cfbuyersclub.org/faqs (accessed April 30, 2021).
[7] Stanojevic S, Vukovojac K, Sykes J, Ratjen F, Tullis E, Stephenson AL. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with Cystic Fibrosis. J Cyst Fibros 2021;20:243–9. doi:10.1016/J.JCF.2020.07.017.
[8] da Silva Filho LVRF, Zampoli M, Cohen-Cymberknoh M, Kabra SK. Cystic fibrosis in low and middle-income countries (LMIC): A view from four different regions of the world. Paediatr Respir Rev 2020. doi:10.1016/j.prrv.2020.07.004.
[9] Medecins sans Frontieres. Untangling the web of antiretroviral price reductions. 2014.
[10] van de Ven N, Fortunak J, Simmons B, Ford N, Cooke GS, Khoo S, et al. Minimum target prices for production of direct-acting antivirals and associated diagnostics to combat hepatitis C virus. Hepatology 2015;61:1174–82. doi:10.1002/hep.27641.
[11] Cooke GS, Simmons B, Miraldo M. Effect of voluntary licences for hepatitis C medicines on access to treatment: a difference-in-differences analysis. Lancet Glob Heal 2019;7:e1189–96. doi:10.1016/S2214-109X(19)30266-9.
[12] Hill AM, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO essential medicines list. BMJ Glob Heal 2018;3:571. doi:10.1136/bmjgh-2017-000571.
[13] Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis c direct-acting antivirals for use in large-scale treatment access programs in developing countries. Clin Infect Dis 2014;58:928–36. doi:10.1093/cid/ciu012.
[14] India Brand Equity Foundation. Pharmaceuticals. 2017.
[15] Panjiva - Global Trade Insights — Panjiva n.d. https://panjiva.com/(accessed February 19, 2021).
[16] 瀚闻资讯 n.d. http://www.sinoimex.com/ (accessed October 1, 2021).
[17] PharmaCompass – Grow Your Pharma Business Digitally n.d. https://www.pharmacompass.com/ (accessed March 12, 2022).
[18] Fortunak J, Ngozwana S, Gebre-Mariam T, Ellison T, Watts P, Emeje M, et al. Raising the Technological Level: The Scope for API, Excipients, and Biologicals Manufacture in Africa. Mak. Med. Africa, Palgrave Macmillan UK; 2016:122–43. doi:10.1007/978-1-137-54647-0_8.
[19] Chaudhuri S, West A. Can local producers compete with low-cost imports? A simulation study of pharmaceutical industry in low-income Africa. Innov Dev 2015;5:23–38. doi:10.1080/2157930X.2014.921273.
[20] Government of India Department of Revenue. TAX RATES. 2021.
[21] Hughes DL. Patent Review of Synthetic Routes and Crystalline Forms of the CFTR-Modulator Drugs Ivacaftor, Lumacaftor, Tezacaftor, and Elexacaftor. Org Process Res Dev 2019;23:2302–22. doi:10.1021/acs.oprd.9b00326.
[22] Export Data and Price of ivacaftor | Zauba n.d. https://www.zauba.com/export-ivacaftor-hs-code.html (accessed November 20, 2021).
[23] List of Drug Master Files (DMFs) | FDA n.d. https://www.fda.gov/drugs/drug-master-files-dmfs/list-drug-master-files-dmfs (accessed November 20, 2021).
[24] World Trade Organisation. Annex 1C Agreement on trade-related aspects of intellectual property rights. 1994.
[25] A generic drug from Argentina offers cystic fibrosis families hope | New Scientist n.d. https://www.newscientist.com/article/2205916-a-generic-drug-from-argentina-offers-cystic-fibrosis-families-hope/ (accessed November 27, 2021).
[26] Morgan SG, Vogler S, Wagner AK. Payers' experiences with confidential pharmaceutical price discounts: A survey of public and statutory health systems in North America. Europe, and Australasia. Health Policy (New York) 2017;121:354–62. doi:10.1016/j.healthpol.2017.02.002.
[27] Barber MJ, Gotham D, Khwairakpam G, Hill A. Price of a hepatitis C cure: Cost of production and current prices for direct-acting antivirals in 50 countries. J Virus Erad 2020;6:100001. doi:10.1016/J.JVE.2020.06.001.
[28] Evaluate. EvaluatePharma ® Orphan Drug. 2019.
[29] Vertex Reports First-Quarter 2021 Financial Results 2021. https://investors.vrtx.com/node/28361/pdf (accessed May 2, 2021).
[30] Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA - J Am Med Assoc 2020;323:844–53. doi:10.1001/jama.2020.1166.
[31] CADTH. Pharmacoeconomic Review Report: Lumacaftor/Ivacaftor (Orkambi). 2018.
[32] Veit G, Roldan A, Hancock MA, da Fonte DF, Xu H, Hussein M, et al. Allosteric folding correction of F508del and rare CFTR mutants by elexacaftor-tezacaftor-ivacaftor (Trikafta) combination. JCI Insight 2020;5. doi:10.1172/JCI.INSIGHT.139983.
[33] Shelton B, Margolis P. The Association of Socioeconomic Status with Outcomes in Cystic Fibrosis Patients in the United States PEDSnet and PCORnet View project Collaborative Chronic Care Network View project n.d. doi:10.1164/ajrccm.163.6.9912100.
[34] Expanded Access | Vertex Pharmaceuticals n.d. https://www.vrtx.com/medicines/expanded-access/ (accessed August 6, 2021).
[35] Amin T. Voluntary licensing practices in the pharmaceutical sector: An acceptable solution to improving access to affordable medicines? 2007.
[36] Zampoli Marco, et al. Global access to affordable CFTR modulator drugs: Time for action!. Journal of Cystic Fibrosis 2022 In press. doi:10.1016/j.jcf.2022.03.006.