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Original Article

Research and development spending versus revenues after approval for CFTR modulators☆

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ABSTRACT

Background: The high prices of CFTR modulators present barriers to access for people with cystic fibrosis (CF), especially those in low- and middle-income countries. Costs of research and development (R&D) are often cited as key drivers of drug pricing. In the case of CFTR modulators, circumstances allow for a meaningful comparison of pre-marketing R&D spending and post-approval product revenues.

Methods: Data on R&D expenditure and CFTR modulator revenues from Q3 2001 (the initial acquisition of CFTR modulator research) until 2024 were extracted from the originator company's Securities and Exchange Commission filings. All values were inflation-adjusted to 2024. Cost of capital was incorporated at a discount rate of 10.5 %, with rates of 7 % and 14 % modelled for sensitivity analysis.

Results: Total out-of-pocket R&D expenditure prior to the successful marketing of elexacaftor/tezacaftor/ivacaftor in Q3 2019 was $18.5 billion. Cost of capital was estimated at $24.8 [13.2–41.6] billion. Actual costs associated with CFTR modulators are likely substantially lower than total R&D spending. Cumulative CFTR modulator revenues from 2012–24 were $63.8 billion, surpassing R&D expenditure in Q2 2020. At over $10.2 billion annually, elexacaftor/tezacaftor/ivacaftor represents one of the highest revenue pharmaceutical products currently on the market.

Conclusion: High revenues mean that R&D costs associated with CFTR modulators have been recouped early in their commercial lifespan. However, their pricing threatens global health equity for people with CF and the financial sustainability of health systems. In the eve of genetic therapies for CF and other rare diseases, sustainable solutions balancing equitable access and financial reward are urgently required.

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1. Introduction

CFTR modulators have revolutionised treatment and outcomes for cystic fibrosis (CF). However, list prices for these lifelong medications lie between $250,000–325,000 per year. When first announced, this pricing model was the subject of significant concern [1], and since then CFTR modulators have been repeatedly deemed not cost-effective by health technology assessors [2]. This has resulted in delays to access and worse outcomes for people with CF (pwCF) in many highly developed economies, such as the United Kingdom, Canada, Australia, and New Zealand [2–4]. And whilst pricing frustrates treatment access in high-income countries (HICs), it renders modulators almost entirely inaccessible in low- and middle-income countries (LMICs) more than a decade after their initial release [5,6].

Accordingly, controversies around pricing have only grown since initial marketing, and are likely to continue following the recent Food and Drug Administration (FDA) approval of vanzacaftor/tezacaftor/deutivacaftor at a wholesale acquisition cost of $379,269 per year [7]. Drug pricing is a notoriously opaque topic, yet a common justification for high prices, and indeed one that has been put forward repeatedly for CFTR modulators, is the need to recover financial costs associated with their research and development (R&D) [8,9].

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Drug development is a long, resource-intensive and inherently risky process, with failure rates of up to 90 % [10]. Therefore, when products are successful, companies must recoup the large sums of money spent over many years on their development. Additional revenue beyond this is required to enable further investment, and companies should be rewarded for taking on risk and innovating, to encourage further breakthroughs. In the case of drugs for rare diseases, often known as orphan drugs, smaller affected populations (and therefore market sizes) necessitate higher per-patient prices to recoup these costs, and further incentives are required lest rare diseases become neglected and excluded from innovation.

There is limited literature evidence relating to R&D costs for CFTR modulators, yet estimates of the cost of developing a novel drug to the point of regulatory approval range from $750 million to $2.87 billion [9, 10]. If applied to the current portfolio of modulators, this would produce a figure of between $3–11.5 billion. However, such studies rely heavily on multiple assumptions and generalised estimates, as seen by the significant variability in their final outputs.

CFTR modulators represent the originator company's first independently developed and marketed class of products, and hold significant overlap in terms of active pharmaceutical ingredient (API). They have now been on the market for over 12 years, and for almost the entirety of this period represented the only products within the company's portfolio and sole source of product revenue. This context enables meaningful comparisons to be drawn between pre-approval R&D spending and post-approval revenues that are not often possible. Accordingly, our analysis aimed to evaluate these metrics for CFTR modulators, and to appraise whether costs of development have been recouped.

2. Methodology

2.1. Sources of data

Data on annual R&D spending and net product revenues for each CFTR modulator were extracted from the Securities and Exchange Commission (SEC) filings of the originator company, Vertex Pharmaceuticals. Importantly, R&D expenditure is reported by the company as an aggregate total, and cannot be stratified into specific projects or product candidates. Accordingly, all data collected reflects total R&D spending of the company for any purpose.

Quarterly 10-Q and annual 10-K filings were used which provide comprehensive, audited financial information for publicly traded companies. All values were inflation-adjusted to 2024 using the Consumer Price Index as listed by the US Bureau of Labour Statistics. Dates of regulatory approval were obtained from the Drugs@FDA database.

2.2. Data inclusion and exclusion

All R&D costs are reported by the company as expenses incurred rather than capital investments, and any outsourced costs to external parties are also included within this metric. In 2022, the company began to separately classify expenditures on collaborations, licensing and acquisitions of third-party technologies and assets as acquired in-process R&D expenses. This separate classification was included within data collection, however mergers and acquisitions of entire external companies were not. All available data on modulator revenues following initial regulatory approval were collected. Other sources of revenue outside of product sales such as technology licensing, instrumentation/biotechnology sales, royalty payments or research collaborations were not included.

2.3. Data analysis

Data collection began from Q3 2001, the quarter of the initial acquisition of the CFTR modulator research portfolio. This therefore represents the earliest possible point from which any portion of R&D spending could be attributed to the development of CFTR modulators. Cumulative R&D expenditure was calculated until an initial endpoint of Q3 2019 (the regulatory approval of ETI and therefore successful marketing). This was selected as ETI was the most recently and widely marketed product at the time of data collection. However, all available data until end of year (EOY) 2024 were collected and analysed. Direct R&D intensity, defined as R&D spending as a proportion of total product revenue, was calculated for each year of complete data as a measure of investment in further innovation.

2.4. Cost of capital

Cost of capital (the opportunity cost of investment over time or potential income if the funds associated with a project had been invested into something else) was modelled as a compounding interest rate applied to annual R&D expenditure. Costs were capitalised at a discount rate of 10.5 % per year in accordance with comparable analyses utilising R&D spending data [9,10]. However, in such studies this is typically incorporated with the endpoint of the regulatory approval and successful commercial release of a single product. Our analysis included multiple entities marketed over a period of seven years, all of which contain at least one overlapping API. Given the nature of our research question and the absence of granular R&D data we therefore opted to utilise an endpoint of 2019 (year of initial ETI marketing) to avoid underestimation.

2.5. Sensitivity analysis

There remains contention over the specific discount rate that should be used when estimating cost of capital, and this extends to the overall inclusion of cost of capital when investigating costs of drug development; with some arguing that it stands to artificially inflate estimates when compared with out-of-pocket expenditure [9]. Accordingly, we also modelled discount rates of 7 % and 14 % for comparison.

3. Results

Total out-of-pocket R&D expenditure from Q3 2001 until Q3 2019 amounted to $18.5 billion, including initial acquisition costs of $1.04 billion (Figs. 1 and 2). Annual R&D expenditure increased at a mean rate of 13.1 % (SD ±19.3) per year from 2002–24. Year-on-year spending increases surpassing one standard deviation from the mean were observed from 2005–06, 2006–07 and 2020–21, and outlying decreases from 2003–04 and 2021–22. Total inflation-adjusted spend to EOY 2024 was $34.3 billion.

R&D intensity fluctuated substantially over the study period. After the commercial release of the company's first marketed product (telaprevir), R&D intensity increased from 56.5 % in 2012 to 175 % in 2014 (Fig. 2). However, this was largely a function of declining sales rather than a real terms increase in R&D investment. As revenues from CFTR modulators grew after 2014, R&D intensity decreased year-on-year to 29 % in 2020, and remained between 30–40 % until the end of the data collection period.

From 2020 the company began to spend considerably more on acquired in-process R&D, totalling $2.43 billion by EOY 2024, compared with $885 million in spending on collaborations and acquisitions prior to 2019. This was largely composed of upfront or milestone payments that markedly influenced results during this period, most notably through a single upfront payment of over $900 million in 2021.

Cost of capital until 2019 was estimated at $24.6 billion, notably larger than out-of-pocket spending. Sensitivity analysis demonstrated that adjustment of the assumed discount rate substantially impacted results. At a rate of 7 %, cost of capital was $13.2 billion, or 46.5 % lower than base estimate. Similarly, using a rate of 14 % increased estimates to $41.6 billion, 68.8 % greater than our base estimate.

No revenue was generated from pharmaceutical product sales prior

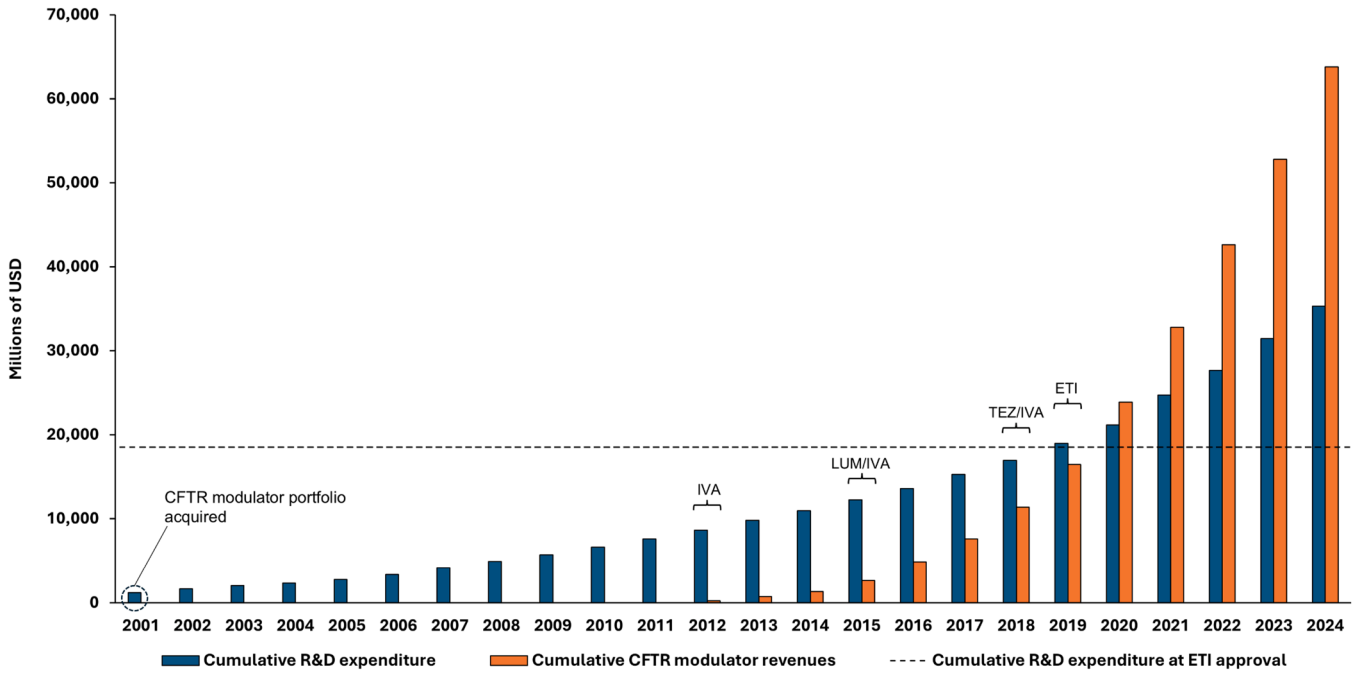

Fig. 1. Graph displaying cumulative R&D expenditure and CFTR modulator revenues from 2001–24. Initial acquisition cost is included and years corresponding to successful initial product launch denoted. All values are inflation-adjusted to 2024. CFTR = cystic fibrosis transmembrane conductance regulator, R&D = research and development, IVA = ivacaftor, LUM/IVA = lumacaftor/ivacaftor, TEZ/IVA = tezacaftor/ivacaftor, ETI = elexacaftor/tezacaftor/ivacaftor.

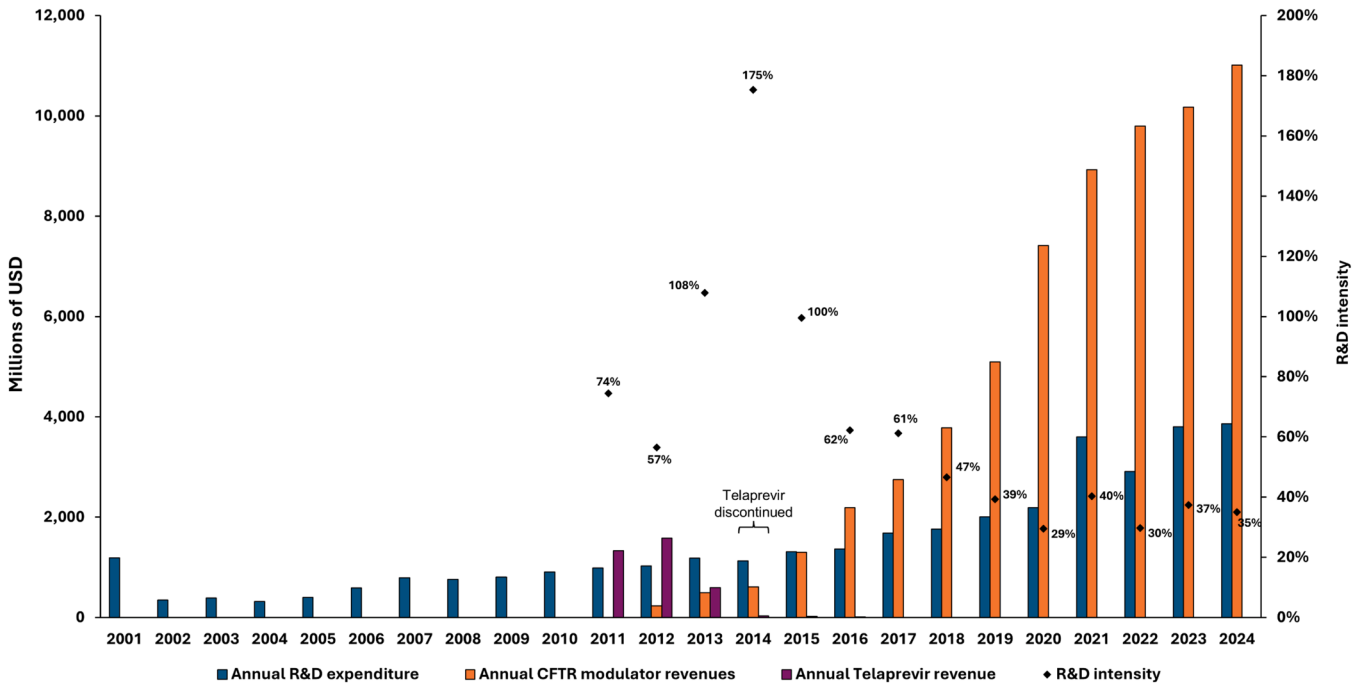

Fig. 2. Graph displaying annual R&D expenditure, product revenues and R&D intensity from 2001–24. Initial acquisition cost is included and all values are inflation-adjusted to 2024. Telaprevir was discontinued in Q4 2014. CFTR = cystic fibrosis transmembrane conductance regulator, R&D = research and development.

to 2011. Initial sales of CFTR modulators began in Q1 2012, and total cumulative product revenues amounted to $63.8 billion by EOY 2024 (Fig. 1). During this time, CFTR modulator revenues increased at a mean rate of 41.9 % (SD ±37.5) per year, compared with 12.5 % (SD ±20.0) for R&D spending over the same period. CFTR modulators represented 94.7 % of the company's total product revenues, with the remaining 5.3 % composed of sales from telaprevir which was marketed in Q2 2011 and subsequently discontinued in Q4 2014. Revenues increased markedly following the regulatory approval of ETI in Q3 2019, with 72.8 % of the company's product revenue generated after this point. Since release, ETI sales have made up a greater proportion of revenue each year, composing 93 % of product sales in 2024. Sales of ETI alone represent 59 % of the company's lifetime pharmaceutical product revenue.

Out-of-pocket R&D expenditure from the point of acquisition of the initial CFTR modulator research portfolio until the release of ETI has

been recouped more than three times over. Cumulative modulator revenues surpassed R&D expenditure in Q2 2020. Over the study period the maximum net cumulative deficit of R&D expenditure versus CFTR modulator revenues was -$9.68 billion, reached at the end of Q2 2015 (Fig. 3). By EOY 2024 this same metric (including all post-ETI R&D spend) showed a surplus of $28.5 billion, equivalent to over seven years of 2024 R&D spending.

In financial year 2024, sales of ETI totalled $10.2 billion, an increase of 122 % from their first full year of revenue in 2020. Notably, entire out-of-pocket pre-marketing R&D expenditure is recouped in just over 20 months of contemporary ETI revenues, and every dollar spent on R&D pre-approval has so far returned $3.45 in modulator revenue.

4. Discussion

This study utilises real-world retrospective, audited financial data and demonstrates that total R&D expenditure, regardless of association with CFTR modulators or even future pipeline medications, is greatly exceeded by the already realised income associated with licensed and marketed CFTR modulators. Our methodology incorporates cost of failure (R&D spending on product candidates that ultimately do not proceed to market), and the inclusion of data until EOY 2024 allows us to account for post-approval spending. It is important to be clear that both the out-of-pocket and capitalised costs attributable to the development of CFTR modulators will be considerably lower than total R&D expenditure. This is especially relevant during earlier years of the data collection period prior to 2013, where the company's primary focus was on treatments for Hepatitis C [11]. For example, the internal budget allocated toward the development of ivacaftor for 2007 was $13.82 million (not inflation-adjusted), equivalent to ~8 % of the company's total R&D expenditure for that year; with a further $4.41 million (~3 %) allocated to research on corrector compounds [12].

There are several key limitations associated with this study. Primarily, a lack of transparent and granular data necessitated utilisation of aggregate R&D expenditure. Accordingly, our results include spending associated with the development of telaprevir and all other product candidates in the company's contemporary pipeline. Several of these have since received regulatory approval and represent new molecular entities in different therapeutic classes, which tend to cost significantly more to develop than next-in-class products [9,13]. Additionally, orphan drug designation (granted to all modulators) can allow for smaller trial sizes, fee waivers and expedited approval, and therefore lower costs of development when compared with non-orphan drugs [13,14]. We also did not account for tax benefits associated with orphan drug development, which can equate to as high as 25–50 % of R&D costs [13,14], or external funding agreements with organisations such as the Cystic Fibrosis Foundation (CFF). Ultimately, the above meant that we were unable to precisely determine historical R&D costs directly associated with CFTR modulators. Yet these limitations would generally lead to over- rather than underestimation of costs, and therefore do not significantly affect our key findings or conclusions. Additionally, use of the regulatory approval of ETI as an endpoint for cost of capital estimates meant that total R&D expenditure was capitalised from early in the company's lifespan for a period of 18 years, significantly longer than the typical estimated length of drug development [15]. Any adjustments to the rate therefore resulted in large changes to final estimates, as demonstrated via sensitivity analysis. This also meant that early R&D spending contributed more heavily to the final estimate, and spending on successfully marketed products continued to be capitalised after their release. Cost of capital is accordingly likely substantially overestimated. Nevertheless, and whichever rate is used, total capitalised R&D costs have been recouped and exceeded early in the commercial lifespan of combination CFTR modulators. It should also be noted that whilst payments for licensing/acquisition of third-party products and assets were usually accounted for as an R&D expense, this was not applied in every instance. However, prior to 2019 such expenditures were generally limited and unrelated to modulators.

The initial pre-clinical research for CFTR modulators was carried out by Aurora Biosciences, with the support of ~$40 million of CFF funding (not inflation-adjusted). This funding remained substantial after the company's acquisition by Vertex Pharmaceuticals, with the CFF agreeing to pay for 70 % of the initial research into corrector molecules from 2006–08, to mitigate the high levels of risk associated with early-stage drug development [12]. This financial support was by all accounts integral to the continuation of research after acquisition, and has led to CFTR modulators representing one of the key exemplars of the venture philanthropy model [11].

For multiple years the originator company generated no product

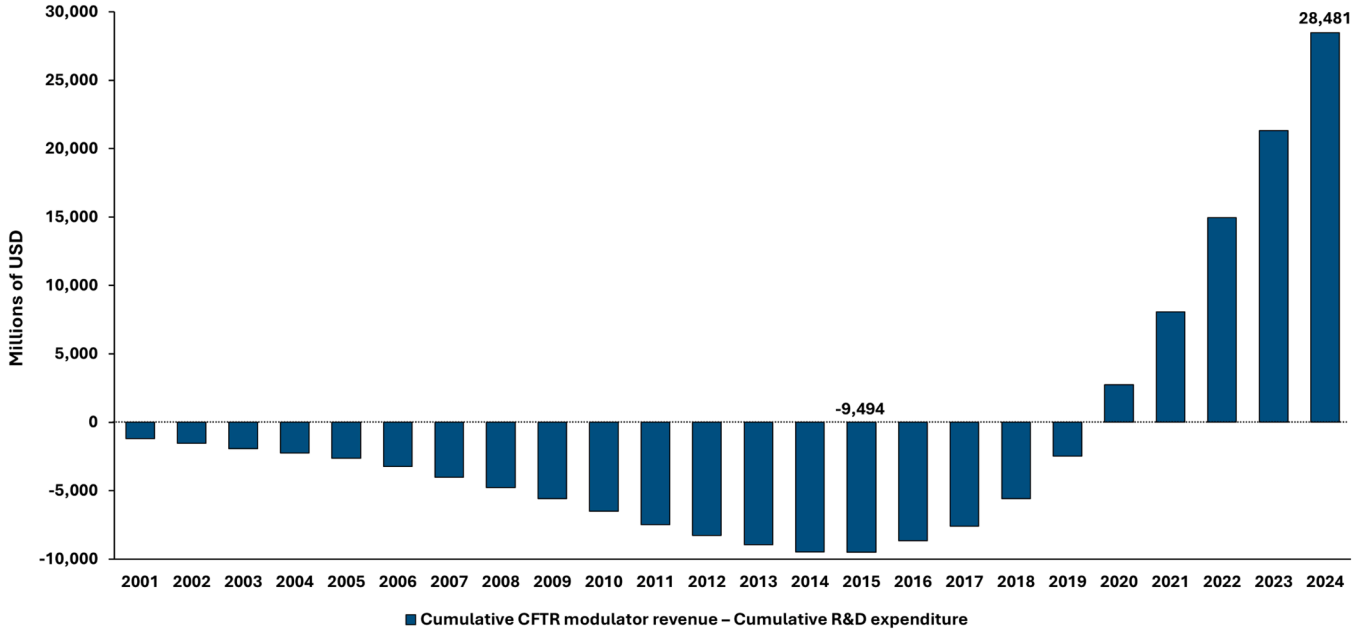

Fig. 3. Graph displaying net difference between cumulative annual CFTR modulator revenues and R&D expenditure from 2001–24. Initial acquisition cost is included and all values are inflation-adjusted to 2024. CFTR = cystic fibrosis transmembrane conductance regulator, R&D = research and development.

revenue whilst continuing to invest in R&D. This is not unusual for an early-stage biopharmaceutical company aiming for growth, and was offset by other sources of income [15]. R&D intensity was highly fluctuant due to the limited number of marketed products across the study period, however after the release of ETI has averaged 35 %, slightly above contemporary estimates of average intensity within the US pharmaceutical industry of 33 % [16]. This was markedly influenced by upfront payments associated with third-party licensing/acquisitions as the company aimed to diversify its portfolio, demonstrated in over $6.5 billion of spending on acquisition of external companies since 2019. Also significant is that our study period only includes four years of ETI sales, with patent exclusivity in place until at least 2037 [17], yet annual revenues are already substantial and comparable to pre-approval out-of-pocket R&D spending. With ongoing label expansions and no competitors outside of early stage trials, it is likely that modulator revenues will continue to grow. However, even assuming that annual revenues were to simply remain at 2024 levels, adjusted for inflation, these would still surpass $206 billion by 2037.

Orphan drug incentives were initially implemented with the rationale of providing increased financial security for risky investments into therapeutic areas that might otherwise be deemed commercially non-viable [14,18]. Yet beyond viability, such medications are increasingly generating substantial revenues, to the extent of becoming "blockbusters" (drugs with revenue of over $1 billion per year) [18]. ETI is emblematic of this phenomenon, representing not only a blockbuster drug, but one of the highest revenue pharmaceutical products currently on the market, despite being sold to less than 70,000 people worldwide (Table 1) [5,19].

Despite negative initial recommendations in health technology assessment, confidential reimbursement agreements for CFTR modulators have now been made in many HICs. Subsequent longitudinal analyses have demonstrated that modulators have driven increases in CF-related healthcare costs to the extent of holding significant wider budgetary impacts, and far outstripping savings from reduced exacerbations and treatment rationalisation [20,21]. For example, from 2018–22 NHS prescription spending on respiratory diseases grew 279 %, from £210 million to £797 million, the largest increase of any therapeutic area. 96 % of this increase was attributable to just three products, and a 115 % growth in spending observed from 2019–20, corresponding with the agreement of a portfolio reimbursement deal for three CFTR modulators [22]. Moreover, such fiscal pressures can be presented even if CFTR modulators are not formally reimbursed; with pwCF in many LMICs gaining access to treatment via legal actions, forcing governments to commit substantial proportions of their health spending to providing medications whose reimbursement had often already been assessed as infeasible [23].

In the context of finite budgets, the opportunity costs associated with reimbursement of such high-cost therapies confer negative impacts on wider population health [24,25]. And with orphan drugs accounting for an increasing proportion of new approvals and health spending [26], the case of CFTR modulators sets a concerning precedent for the pricing of future therapies for CF and other rare diseases, and poses a threat to the financial sustainability of health systems. Such resource allocation challenges are likely to disproportionally affect LMICs, and are underscored by the advent of genetic therapies with even higher anticipated price tags. This is exemplified by the recent approval of exagamglogene autotemcel, a $2.2 million genetic therapy for sickle cell disease, which represents another of the most prevalent genetic diseases worldwide, and a condition wherein the majority of the disease burden lies in LMICs [27].

The development of similar therapeutic options for pwCF who remain ineligible for current generation modulators, and the expansion of clinical trials in LMICs where such mutations are more frequent, constitute top CF research priorities [28]. However, these too will likely be hindered by contemporary disparities in treatment access, as significant ethical challenges would be posed in asking patients to assume the risks of a trial if they may not stand to benefit from the results [29,30].

Clearly, sustainable solutions are required that balance financial reward with equitable access. In 2023, the originator announced a donation program for ETI in 14 countries [5]. Yet, two years later, there remains little to no tangible information regarding the scope, sustainability, governance or impact of this initiative; and in any case philanthropy is not an effective or sustainable solution to lack of access to medicines in poorer countries - especially for diseases requiring lifelong treatment [31].

To this end, voluntary licensing, wherein manufacturers in resource-limited areas are authorized to sell generic versions of patented medications at close to cost price, has been a key policy used successfully in multiple therapeutic areas, and by many of the world's leading pharmaceutical companies, without hindering innovation or growth [32]. Indeed, it appears equally viable in this setting; with research indicating that minimum production costs for CFTR modulators could lie as low as $6000 per year of treatment, multiple companies already marketing generic modulators at greatly reduced prices and internal estimates by the manufacturer that prices will fall by up to 90 % after patent expiry [4,17]. However, this approach is reliant on the collaboration of the patent holder. Where this is not forthcoming, and treatment access deemed necessary to protect public health, governments retain the authority to overturn patents and permit generic manufacture via compulsory licensing, a measure with precedent in both CF and other disease areas [23,33].

Ultimately, beyond individual policy tools, in the era of precision medicine fair pricing and equitable access must become a firm international priority.

Table 1
Table of the ten highest global revenue pharmaceutical products in 2024 [19]. Generic names are used with brand names listed in brackets. Revenue data extracted from SEC filings and earnings reports. Indications are listed as per the most recent available label on the US Food and Drug Administration database. HIV = human immunodeficiency virus, MHRA = Medicines and Healthcare products Regulatory Agency.

Product	2024 global revenue (millions of USD)	Initial approved indication	Number of FDA approved indications	Registered as orphan drug by MHRA
Pembrolizumab (Keytruda)	29,482	Malignant melanoma	21	No
Semaglutide (Ozempic)	17,466	Type 2 diabetes mellitus	1	No
Dupilumab (Dupixent)	14,148	Atopic dermatitis	6	No
Bictegravir/ emtricitabine/ tenofovir (Biktarvy)	13,423	HIV	1	No
Apixaban (Eliquis)	13,333	Prophylaxis of stroke in non-valvular atrial fibrillation	5	No
Risankizumab (Skyrizi)	11,718	Plaque psoriasis	4	No
Daratumumab (Darzalex)	11,670	Multiple myeloma	1	Yes
Tirzepatide (Mounjaro)	11,540	Type 2 diabetes mellitus	1	No
Ustekinumab (Stelara)	10,361	Plaque psoriasis	4	No
Elexacaftor/ tezacaftor/ ivacaftor (Trikafta)	10,239	Cystic fibrosis	1	Yes

5. Conclusion

Out-of-pocket R&D costs for CFTR modulators have been recouped multiple times over. Prohibitively high prices are likely to remain the primary barrier to access for CFTR modulators, while rendering ETI one of the highest revenue contemporary pharmaceutical products. It is apparent that equitable access to treatment is feasible without jeopardising further innovation. It is vital that transformative discoveries are rewarded, but this cannot and need not come at the cost of the health and lives of people with CF.

Ethical approval

No ethical approval was required as this analysis used only publicly available information and no patient data.

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Data sharing statement

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

CRediT authorship contribution statement

Jonathan Guo: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Grace Hennessy:** Validation, Investigation, Data curation, Writing – review & editing. **Benedict Young:** Visualization, Writing – review & editing. **Andrew Hill:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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