Pay-for-performance pricing for a breakthrough heart drug: learnings for cell and gene therapies

“Novartis’ pay-for-performance deals for its breakthrough heart failure small-molecule product Entresto are a major step in making the world clearer...”

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The high and growing cost of drugs has caused deep public, physician, healthcare payer and political concern in recent years. In 2014, drug expenditure in the USA grew by 13% to reach US\$374 billion, the largest percentage point increase since 2001 [1]. Front runners in November’s USA presidential race have even gone so far as to propose that Medicare, the federal government’s health insurance program primarily for older adults and which is America’s single largest health insurer, should be able to negotiate drug prices with pharmaceutical companies [2]. This is noteworthy given that unlike in Europe, the USA does not have a tradition of government price controls on medicines. One approach that can potentially be used to help address the problem of high drug costs is pay-for-performance agreements between pharmaceutical companies and healthcare payers, whereby payment for a drug upon market entry is tied to how well it performs in real-life patients (as judged by an appropriate outcome).

Toward the beginning of 2016, Novartis (Basel, Switzerland), a leading global pharmaceutical company, entered into pay-for-performance deals with two of America’s leading health insurers, Cigna (CT, USA) and Aetna (CT, USA), for its novel heart failure drug Entresto [3], which is an orally administered, small-molecule product, combining sacubitril, a first-in-class neprilysin inhibitor and valsartan, an older angioten-

sin II receptor blocker first approved in the 1990s. Entresto was approved by the US FDA in July 2015 for heart failure on the basis of its ability to reduce the rate of cardiovascular death and heart failure hospitalizations. The pay-for-performance agreements are based on a base price for Entresto and a modest rebate that will vary according to drug performance.

Novartis’ deals may end up being a game changer in the widespread utilization of pay-for-performance agreements for two reasons. First, performance-based deals have rarely been used in the USA [4], in large part due to the potential difficulties in implementing them, owing to the costs and complexities in tracking health outcomes/measures in patients in the real world. However, with Entresto, Novartis has been successful in forging performance-based deals with leading USA health insurance companies (and other insurers could potentially follow suit). Second, Entresto is anticipated to be a major drug for Novartis going forward, with predicted global peak sales of US\$5–10 billion/year [5]. Any pricing strategy that significantly helps to generate that level of commercial success will be viewed highly favorably by the pharmaceutical industry.

When considering cell and gene therapies, one must appreciate that they do not exist in isolation and will very much be affected by pertinent events occurring in the wider pharmaceutical industry. Hence,

the concern around the high cost of small molecule and monoclonal antibody drugs will also be directed at cell and gene therapies, potentially even more so, given that they are as a matter of course anticipated to have upfront treatment costs that are high (US\$50,000–100,000+/patient for one or a small number of doses given over a few weeks or months) or ultra-high (US\$500,000–1 million+/patient) [6,7]. The field of genetically modified T-cell cancer therapies is widely considered to be the most promising area in oncology R&D right now and such therapies are expected to be priced around US\$450,000–500,000/patient [8,9]. It is clear that cell and gene therapies are in line to come under a high level of scrutiny from healthcare payers, physicians, patients and politicians in terms of their price, and companies seeking to develop and commercialize them can learn four key lessons from Novartis' pay-for-performance deals for Entresto.

“...healthcare payers are most likely to be interested in pay-for-performance deals where payment is linked to an outcome that has a direct positive economic impact for them...”

First, Entresto is priced at around US\$4500/patient/year, it demonstrated outstanding clinical results, and has been described as ‘one of those once-in-a-decade kind of breakthroughs’ [10]. The drug cut the risk of cardiovascular death or heart failure hospitalizations by 20% versus the standard of care (enalapril, an angiotensin-converting enzyme inhibitor) in its pivotal clinical study (named PARADIGM-HF), which was stopped early due to remarkable results [11]. It is crucial to appreciate that despite Entresto having a relatively low price (compared with, e.g., new cancer drugs, which cost around US\$100,000/patient/year [12]) and outstanding clinical results, Novartis considers pay-for-performance to be the optimal pricing model to pursue for the drug [4], signaling that the pay-per-pill model traditionally used by the pharmaceutical industry is a less viable choice in present times. Approximately 2.2 million Americans with heart failure, who are presently treated with a cheap generic medicine, are potentially eligible for Entresto [11], so its impact on health budgets, even at a price of US\$4500/patient/year, could be significant. The pay-for-performance approach should help Novartis maximize sales by striking a balance between drug price and volume sold. Having an effective price–volume strategy will also be critical for the commercial success of a cell or gene therapeutic.

The message for cell and gene therapies is clear: risk-sharing agreements are likely to be needed with both higher price, lower volume and lower price, higher volume products, even when clinical studies generate remarkable or curative results. This may end up having

significant repercussions for the field of T-cell cancer therapies, where experimental medicines have to date shown unprecedented clinical study results in hematological malignancies. For instance, complete remissions in 90% of individuals with relapsed/refractory acute lymphoblastic leukemia [13] and sustained remissions ongoing past four and a half years in relapsed/refractory chronic lymphocytic leukemia [14] have been demonstrated.

Second, the outcome forming the basis of the pay-for-performance deals for Entresto – that is, a reduction in the proportion of patients hospitalized for heart failure [3] – has a direct economic impact in terms of cost savings for the health insurer. It is telling that a surrogate outcome (e.g., improvement in ejection fraction of heart failure patients) or a purely clinical outcome (e.g., survival benefit) has not been agreed. This signals that to be attractive to healthcare payers, pay-for-performance deals with cell and gene therapies will likely need to be based on an outcome that has a clinically meaningful as well as a positive economic impact.

Third, the primary end point in the pivotal study of Entresto was a composite of cardiovascular death or heart failure hospitalization (which has direct economic repercussions) [15]. The learning here is that companies taking cell and gene therapies into pivotal studies need to carefully consider whether a coprimary end point where one measure has direct economic implications (e.g., a reduction in hospitalizations or costly complications) would be best.

Fourth, the pay-for-performance deals are primarily based upon replicating clinical results achieved with the coprimary end point of heart failure hospitalizations in the pivotal study of Entresto in the real-world setting. This approach of reproducing clinical study results in real-life patients is expected to gather healthcare payer, physician, public and political support, and may become the standard that new medicines (including cell and gene therapies) are held up to upon market entry.

A strong message for companies seeking to successfully commercialize cell and gene therapies is emerging: risk-sharing agreements will almost certainly be needed, even when outstanding results are achieved in clinical studies; healthcare payers are most likely to be interested in pay-for-performance deals where payment is linked to an outcome that has a direct positive economic impact for them; including an economic focused outcome as a coprimary end point may make sense; and receiving a desired level of payment for a medicine will more than likely be contingent upon replicating clinical study results in the real-world setting. Novartis' pay-for-performance deals for its breakthrough heart failure small-molecule product Entresto are a major

step in making the world clearer in terms of the reimbursement landscape that cell and gene therapies may ultimately face. Indeed, one may speculate that given its interest in pursuing and subsequently being triumphant in securing pay-for-performance agreements for Entresto, Novartis may seek to forge performance-based deals for its highly anticipated CAR T-cell cancer therapy, which is expected to be the first T-cell cancer immunotherapy to be approved, perhaps as early as 2017 [16]. Hence, Novartis could end up leading the way for the cell and gene therapy industry with regard to pricing models for commercialization.

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