EDISON

Trial outcomes and value

Explaining contemporary clinical trial issues

Edison themes

1 April 2019

For recently approved drugs with premium prices, healthcare budgets are being stretched and are likely to be rationed in one form or another. To justify the value of the drug, companies have to invest more on measuring their drug's benefit or outcomes. For companies developing one-off treatments such as gene and cellular therapies, there are expectations that a single price per treatment course will capture the value of a lifetime cure. Here we explore how some clinical trials are now measuring outcomes and endpoints for both small molecules and innovative therapies.

How does a clinical trial translate into value?

Until recently, a positive well-controlled Phase III programme conducted in a large number of patients would usually lead to commercial success, despite the patent position. These days, a positive clinical trial is far from guaranteed to translate into commercial success in many indications and drug sponsors are having to do things differently to demonstrate value to payers. This is even more acute as cheap generic drugs comprise the standard of care in many indications and the unmet medical needs are in smaller, higher value, more difficult to treat patient populations.

Innovative therapies mean innovative pricing

The approval of drugs with very high prices and innovative cell and gene therapies that are proposed to be priced as millions of dollars per treatment magnify this issue of demonstrating value. Innovative therapies are giving rise to innovative pricing mechanisms that invariably involve measuring to demonstrate value. This is easier said than done.

Likely winners

- **Clinical research organisations (CROs)** such as Parexel, IQVIA and ICON, which have added long-term outcome studies to their product offerings.
- **Pharma and biotech companies** that able to provide positive outcome data.
- **Payers,** which have to sit back and wait for outcome data before reimbursing.
- **Patients,** who are more likely to receive drugs that provide them a benefit.

Likely losers

- **Pharma and biotech companies** that cannot show positive outcomes.
- **Whoever collects the data:** if small pharma and biotech companies have to collect outcomes data and follow patients in registries to be reimbursed, their costs will go up.

Winners and losers: The companies shown above do not translate into buys and sells as other themes (and valuation parameters) may conflict with this one.

Viewpoint

Clinical trials, particularly later-stage Phase II or III studies, are among the most expensive investments in R&D a life science company can make. This investment is often greater than the capital expenditure needed to manufacture the product to commercial scale but it is granted a tax break in most jurisdictions. With clinical trials providing the foundation on which the commercial success of the company is based, it is not surprising the announcement of these results is associated with stock volatility. After many decades of modern medicine, the low-hanging fruit of easier to discover drugs have already been picked and many of today's clinical studies are even higher risk because they are conducted in more difficult-to-treat indications. If those products require expensive and additional outcome studies to justify their high pricing, then the clinical and commercial risks will increase.

Edison themes

As one of the largest issuer-sponsored research firms, we are known for our bottom-up work on individual stocks. However, our thinking does not stop at the company level. Through our regular dialogue with management teams and investors, we consider the broad themes related to the companies we follow. Edison themes aims to identify the big issues likely to shape company strategy and portfolios in the years ahead.

Analyst

Andy Smith +44 (020) 3077 5700

healthcare@edisongroup.com

Edison has conducted pricing and market access studies with payers for its clients where a pricing corridor from a Van Westendorp analysis and estimations of market penetration have been determined after presenting and discussing the target product profiles of the drugs. We have used these inputs to better inform out valuation models for our clients' products.

Clinical trials, outcomes, value and pricing

Clinical trial definitions: Endpoints and outcomes

The announcement of clinical trial results by biotech and pharma companies is frequently associated with sometimes extreme share price volatility if success or failure is unexpected. When AstraZeneca reported the long-anticipated clinical trial result for its checkpoint inhibitor Imfinzi in first-line lung cancer, which failed to improve overall survival, the company lost $14bn from its market capitalisation. Therefore, the determination of success or failure is initially made by the market when investors interpret the primary and secondary endpoints of the study. There is significant debate on whether the meeting of a primary endpoint to an accepted level of statistical significance in an overpowered study (one that enrols many hundreds of patients to measure a small effect) is clinically or commercially significant. So, starting with mainstream indications and drugs for diabetes, for example, we will first define what an endpoint is, and explain how it differs from the more robust outcome, then discuss how outcomes are more likely to result in commercial success.

Endpoints are numerical evaluations of an effect of a drug or device on a clinical trial population. For a study to be successful, the active arm must be more efficacious in the primary endpoint measurement than the placebo arm by a sufficient margin to be statistically significant (ie a low probability the result occurred by chance). When this occurs, the primary efficacy endpoint can be said to have been met. An example of a pragmatic, hard clinical endpoint is overall survival (OS) after five years in a cancer clinical trial. It is easy to measure and the value of returning a patient to the workforce is considerable. But measuring this particular endpoint can take much longer than five years because not all patients are enrolled at the same time and, as a result, the cost of the study is very high. Endpoints that are related to OS, such as progression-free survival, are often used to achieve regulatory approval more quickly than if OS had been the primary endpoint. Although all this is logical, clinical trial endpoints in many other non-oncology disease indications are much less pragmatic and are linked to, or are only indicative of, hard clinical effectiveness endpoints. These are called surrogate endpoints and are part of an emerging issue that links innovative therapies and value.

Surrogate endpoints

In diabetes patients, for example, a primary surrogate endpoint (on which the success of a trial is judged) is almost always a reduction in either fasting plasma glucose (FPG) or glycosylated haemoglobin (Hb1Ac) and their maintenance below a target level more associated with that seen in non-diabetic patients. This endpoint is almost always measured against a matched and randomised group of patients that receive a placebo and the study sponsor's goal is that this arm does not show the significant reductions in FPG or Hb1Ac that are observed in the active arm of the study. Although well accepted by the FDA[1] for the purposes of approving anti-diabetic drugs, the surrogate endpoints of FPG and Hb1Ac only imply a clinical benefit rather than actually measuring a more tangible clinical effect of (what would be the failure of) anti-diabetic medicines, such as lower limb amputation, blindness or death. Surrogate endpoints such as these are used to approve anti-diabetic drugs because the time, cost and ethics of running a study to measure these tangible health outcomes have been too great or unacceptable for patients in the placebo arm. Even the measurement of intermediate outcomes of diabetes[2] such as proteinuria, retinopathy or foot ulcers may be unethical because it would result in some deterioration in the health of the patients

[1] www.fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf.

[2] www.ncbi.nlm.nih.gov/pubmed/11965832

(particularly in the placebo group) during the study and may not be easily reversed. This is unless the placebo arm patients are treated with the existing standard of care and the active arm seeks to lower the rate of these intermediate or even final outcomes.

Primary endpoints

The primary endpoint (whether surrogate or clinical) is usually the key measure of a clinical trial that might, if achieved, result in the regulatory approval of the drug, although this may lead to commercial success. The drug sponsor's choice of primary endpoint should be one that is widely accepted as a validated measure of clinical efficacy and that choice should hopefully be discussed and agreed with the regulators before the study starts (a prospectively-defined primary endpoint). Unfortunately, unless the FDA agrees it in a special protocol assessment (SPA) or its equivalent with the European Medicines Agency (EMA) prior to the commencement of the clinical study, there is usually no commitment for a regulator to approve a drug on the basis of a drug sponsor's choice of primary endpoint. In some cases, even when an SPA has been agreed, changes to the study or the standard of care have invalidated it. Some hypothetical examples of met and missed endpoints and their impact on the approvability of a drug are illustrated in Exhibit 1. In the case of diabetes, for example, secondary endpoints can be the reduction in the amount of insulin used when testing oral anti-diabetic drugs or the patients' weight gain, and are useful supportive measures of the drug's value.

Exhibit 1: Estimated approvability based on clinical trial results

Reported results	Drug #1	Drug #2	Drug #3	Drug #4	Drug #5
Primary efficacy endpoint	Met	Met	Missed	Missed	Missed
Secondary efficacy endpoints	Met	Most met	Some met	Most missed	Most missed
Safety endpoints	~placebo	Worse than placebo	~placebo	~placebo	Worse than placebo
Retrospective endpoint analysis	No	No	No	Yes	No
Retrospective subgroup analysis	No	No	No	No	Yes
Comment on approval	Ideal result	Almost ideal	Difficult	Unlikely	Highly unlikely

Source: Edison Investment Research

Take-home point on approvability: Look for a statistically significant difference in primary endpoint between the active and placebo arms. This may be sufficient for regulatory approval, but commercial success will depend on the size of the effect, over the competition, whether the competition is generic and the price differential between the new drug and the standard of care .

The moving goalposts in endpoints and value

For many drugs with well-accepted endpoints such as weight loss in obesity or Hb1Ac in diabetes, these endpoints, although likely to result in approval of the drug, may not result in commercial success if their efficacy is on a par with the accepted standard of care for that condition. This is truer now the accepted standard of care for many indications is generic and very cheap. In the US, commercial payers will put reimbursement algorithms in place to restrict access to new expensive drugs unless patients have failed to respond to cheaper drugs that are probably as efficacious in many patients. Enter the outcome study, where a drug sponsor will choose to conduct a study aimed at demonstrating a tangible clinical effect or outcome. In these cases, the outcomes measured could be a reduction in death or major adverse cardiovascular events (MACE; a stroke or heart attack) so its drug is differentiated from others that have only been shown to reach a surrogate endpoint.

Regulators originally demanded outcome studies after initial approval to show a drug did not have a detrimental effect (negative outcome such as liver failure or higher MACEs than placebo) that would not have been observed in the smaller studies comprising the original marketing application. Some pharmaceutical companies have turned this onerous and expensive outcome study requirement into a route that not only differentiates their drugs from other products, but also justifies higher prices.

Returning to diabetes, many years of modern drug discovery and development have resulted in a large number of anti-diabetic drug classes, some of which are now generic and some, such as insulin and the glucagon-like peptide receptor agonists (GLP-1), are large-molecule branded drugs. For any new anti-diabetic drug likely to be used in very large patient populations, the FDA and EMA would usually demand a large cardiovascular outcome study to determine the drug does not have an overall negative effect on the patient population. But before this requirement came into force, a number of companies chose to conduct cardiovascular outcome studies to give their products an edge over the competition. Only five branded anti-diabetic drugs, three in the sodium-glucose co-transporter (SGLT2) inhibitor class and two GLP-1 receptor agonists, have demonstrated positive mortality benefits (fewer deaths on the active drug arm than the placebo arm) in outcome studies. This long-term positive mortality benefit (rather than meeting a surrogate or other endpoint) is what is required to demonstrate an economic benefit to payers and in consequence have the best chance of commercial success. These two anti-diabetic drug classes with positive outcome studies command higher prices in most markets than, for example metformin and the dipeptidyl peptidase-4 (DPPIV) inhibitors, which have not demonstrated mortality benefits but are very cheap and effective at lowering blood glucose.

Take-home point: for drugs in a competitive environment, positive outcome studies can be a key, although costly, differentiator. For small-molecule drugs, where the risks of off-target effects may lead regulators to require outcome studies as a contingent step to full approval, the risk of a negative outcome is also present.

Outcomes-based pricing comes to new drugs

The advantage of the so-called innovative therapies of cell and gene therapies is that one dose or course is expected to result in the patient being cured. As a result, the patient can return to the workforce and their payer can save the cost of many years of expensive therapy. For a cancer therapy, the outcome and endpoint can be the same, five-year OS for example, and if measured for long enough, will determine the real value of the product. When the first CAR-Ts were approved, the survival data from clinical trials were reasonably immature and payers found themselves in a position of being asked to reimburse $475,000 for a treatment course on the basis of only nine months of data.

The thin edge of this wedge started in small molecules that are not gene or cellular therapies. In 2015, Novartis launched Entresto (valsartan/sacubitril) in July 2015 as a treatment for heart failure (HF) patients, initially at a wholesale acquisition cost of $4,560 per patient per year. A similar cost for a generic treatment for HF patients is about $48 per patient per year. Not surprisingly, Entresto sales were sluggish as payers in the US put the barriers of prior authorisation and step edits in the way of the market access for Entresto. Entresto's first half-year sales were only $21m. A subsequently positive cardiovascular outcomes trial (CVOT) that demonstrated a mortality benefit for Entresto over a generic angiointensin-converting-enzyme inhibitor used in HF patients and Entresto's inclusion in the American College of Cardiology and American Heart Association guidelines for the management of HF patients were not enough to increase adoption until 2016, when Novartis negotiated outcome-based pricing contracts for Entresto. Novartis agreed to reduce the price of Entresto initially to two individual payers if the outcome of HF hospitalisation exceeded a pre-specified threshold that was in line with the drug's approved label.[3] Although it took until 2018 to impact sales, in October that year Novartis increased its FY18 guidance based on the performance of Entresto, the sales of which had more than doubled in Q318 to $271m compared to Q317.

It appears that outcomes and pricing now go hand in hand for expensive, newly launched products, especially when there is competition. When the FDA approved the first proprotein convertase

[3] www.managedhealthcareexecutive.com/managed-healthcare-executive/news/novartis-signs-value-based-pricing-entresto

subtilisin/kexin 9 inhibitor (PCSK9i) in 2015 for lipid lowering in heterozygous familial hypercholesterolemia patients, the launch list price was about $14,000 per year and sell-side expectations were for a blockbuster. Despite a subsequent net price closer to $9,000 a year, a positive CVOT two years after launch and a label expansion for the prevention of MACEs, payers continued to restrict sales. The 2017 global sales of the first PCSK9i, Sanofi's Praluent (alirocumab), and the second to launch, Amgen's Repatha (evolocumab), were only $194m and $319m respectively. In 2018 the manufacturers of both approved PCSK9is reduced their prices to $5,850 per year and sales increased by 47% and 72%, respectively.

Innovative medicines bring new challenges

After a series of failures between the mid-1990s and the mid-2000s, gene therapy drugs started to come back from obscurity as clinical trials resumed. The world's first gene therapy, Glybera, was approved in Europe in 2012 in a very small patient population and came with a headline-grabbing €1m price tag. Glybera's use was limited to a few patients in Germany but was never reimbursed at the proposed price and it was eventually withdrawn from the market in 2017. It was not the most auspicious of starts for gene therapy. In 2010 a collaboration between GlaxoSmithKline (GSK) and an Italian institute resulted in a gene therapy product development, also for a very rare disease – severe combined immunodeficiency due to adenosine deaminase deficiency – with only 15 patients a year in Europe. This drug, Strimvelis, was approved by the European Medicines Agency in 2016, launched by GSK at a price of €594,000 but spun-off into a new company, Orchid Therapeutics, in April 2018.

The companies (mainly biotechnology) that have developed these innovative therapies to the point of regulatory approval have recently been a rich source of M&A transactions, with chimeric antigen receptor T-cell therapy (CAR-T) companies Kite and Juno acquired in 2017 for $12bn and $8bn, respectively. In 2019, pure-play gene therapy companies Spark Therapeutics and Nightstar Therapeutics are being acquired for $4.8bn and $877m, respectively. CAR-T involves immune cells extracted from a patient that are genetically engineered in vitro, and then re-infused back into the original patient in an autologous cell transplant. This type of innovative therapy has the advantage of not provoking a rejection when it is re-infused back into the patient (although efficacy and even the pre-conditioning regimen are associated with serious, and sometimes fatal, side effects). The genetic manipulation of CAR-T cells requires small amounts of vector because it is conducted ex vivo in the lab rather than vector administered systemically. The first FDA approval of a gene therapy was at the end of 2017. Luxturna from Spark Therapeutics (recently acquired by Roche) is a corrective gene therapy where the (low dose of) vector is injected directly into the back of the eye. Luxturna was priced at $850,000 for a single dose to both eyes and raised the question of how much these innovative therapies are worth. Spark recorded $27m in Luxturna in its first full year on the market. With headline-grabbing 'sticker shock' prices in the millions of dollars suggested as the price for these 'once-and-done' therapies, the focus from payers has started to rest on the value of the outcomes generated.

The impact of pricing issues for innovative therapies

For innovative gene and cellular therapies, where the pricing is hundreds of thousands of dollars or more, innovative pricing agreements that take into account payment according to outcomes has become a topic of discussion. Innovative pricing strategies are any agreement between a manufacturer and a payer that moves beyond the simple single price per pill, with no selection of the patients to be treated. At one end of this spectrum of pricing agreements are the options that limit the total financial risk of the payers, for example agreeing a total drug cost for all the patients covered by that payer. An example here would be the proposal by the UK's National Institute for Health and Care Excellence (NICE) to limit the total exposure of NHS England to £500m to treat all eligible English cystic fibrosis (CF) patients over five years in return for allowing the US biotech

company Vertex to sell its drugs for CF in England. Vertex has rejected NICE's proposal as its combination drug has a list price in the US of $272,000 and NICE's proposal for access to the about 8,000 English CF patients represented about half the US price. NICE has determined that Vertex's drugs are not cost effective at even the originally proposed UK prices.

Despite the ongoing arguments on cost effectiveness, there have been no details of any outcome-based measures in the NICE proposal to Vertex. In contrast, contracts based on outcomes and risks are front and centre in the debate on the reimbursement of cell and gene therapies. This is because the proposed cost per patient is so high for some gene therapies, the duration of the outcomes is uncertain and healthcare budgets are typically annual, rather than being apportioned over the lifetime of a patient. As a result, GSK has already given a money-back guarantee for its €594,000 gene therapy product Strimvelis in Europe and Novartis is considering an outcomes-based price model for its $475,000 CAR-T product, Kymriah. In the latter case, the duration of the response to the therapy or the length of the cure to the patient would lead to incremental payments, perhaps annually, based on its continued success. In central-payer markets such as the UK, where patients can be closely followed, this is not likely to be difficult but in much larger fragmented markets such as the US, where patients can move jobs (and therefore health insurers) across the country, monitoring the duration of their responses and therefore the reimbursement to the drug manufacturer could be problematic.

Where there's a will, there will be a way

Moving away from the traditional per-pill drug pricing model will be an uncomfortable reality for many pharmaceutical and biotechnology companies and their investors, who will need to adjust the ways they value the products. But the paradigm for innovative gene and cellular therapies is different to that of the traditional drug pricing models, in that a small patient population is treated once with an innovative therapy and that the price of a single treatment will have to recoup many years of investment by the drug sponsor and reflect the total subsequent healthcare cost to the payer, had that patient not been treated with an innovative therapy. This brings the big-ticket sticker shock to payers that would like to offer the therapy to their patients but, even with small patient populations, are unable to do so within the constraints of their annual budgets. On one side, there is unlikely to be a cheap standard of care with which to compare cell and gene therapies, but on the other both the drug sponsors and payers will have to find a way to structure reimbursement so that the investment is appropriately rewarded. Whether the innovative pricing strategies confine the treatment to a (probably) genetically defined patient population, contractual arrangements capping the annual drug cost to the payer, or contacts based on long-term outcomes, these arrangements will have to be negotiated between drug manufacturers and payers. For every problem there is supposedly an answer and innovative pricing strategies, and the negotiations on which they are based, appear to be the most likely answer to help pay for these innovative medicines.

General disclaimer and copyright

This report has been prepared and issued by Edison. Edison Investment Research standard fees are £49,500 pa for the production and broad dissemination of a detailed note (Outlook) following by regular (typically quarterly) update notes. Fees are paid upfront in cash without recourse. Edison may seek additional fees for the provision of roadshows and related IR services for the client but does not get remunerated for any investment banking services. We never take payment in stock, options or warrants for any of our services.

Accuracy of content: All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report and have not sought for this information to be independently verified. Opinions contained in this report represent those of the Edison analyst at the time of publication. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations.

Exclusion of Liability: To the fullest extent allowed by law, Edison shall not be liable for any direct, indirect or consequential losses, loss of profits, damages, costs or expenses incurred or suffered by you arising out or in connection with the access to, use of or reliance on any information contained on this note.

No personalised advice: The information that we provide should not be construed in any manner whatsoever as, personalised advice. Also, the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The securities described in the report may not be eligible for sale in all jurisdictions or to certain categories of investors.

Investment in securities mentioned: Edison has a restrictive policy relating to personal dealing and conflicts of interest. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report, subject to Edison's policies on personal dealing and conflicts of interest.

Australia

Edison Investment Research Pty Ltd (Edison AU) is the Australian subsidiary of Edison. Edison AU is a Corporate Authorised Representative (1252501) of Myonlineadvisers Pty Ltd who holds an Australian Financial Services Licence (Number: 427484). This research is issued in Australia by Edison AU and any access to it, is intended only for "wholesale clients" within the meaning of the Corporations Act 2001 of Australia. Any advice given by Edison AU is general advice only and does not take into account your personal circumstances, needs or objectives. You should, before acting on this advice, consider the appropriateness of the advice, having regard to your objectives, financial situation and needs. If our advice relates to the acquisition, or possible acquisition, of a particular financial product you should read any relevant Product Disclosure Statement or like instrument.

New Zealand

The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are "wholesale clients" for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a "personalised service" and, to the extent that it contains any financial advice, is intended only as a "class service" provided by Edison within the meaning of the FAA (i.e. without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision.

United Kingdom

Neither this document and associated email (together, the "Communication") constitutes or form part of any offer for sale or subscription of, or solicitation of any offer to buy or subscribe for, any securities, nor shall it or any part of it form the basis of, or be relied on in connection with, any contract or commitment whatsoever. Any decision to purchase shares in the Company in the proposed placing should be made solely on the basis of the information to be contained in the admission document to be published in connection therewith.

This Communication is being distributed in the United Kingdom and is directed only at (i) persons having professional experience in matters relating to investments, i.e. investment professionals within the meaning of Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "FPO") (ii) high net-worth companies, unincorporated associations or other bodies within the meaning of Article 49 of the FPO and (iii) persons to whom it is otherwise lawful to distribute it. The investment or investment activity to which this document relates is available only to such persons. It is not intended that this document be distributed or passed on, directly or indirectly, to any other class of persons and in any event and under no circumstances should persons of any other description rely on or act upon the contents of this document (nor will such persons be able to purchase shares in the placing).

This Communication is being supplied to you solely for your information and may not be reproduced by, further distributed to or published in whole or in part by, any other person.

United States

The Investment Research is a publication distributed in the United States by Edison Investment Research, Inc. Edison Investment Research, Inc. is registered as an investment adviser with the Securities and Exchange Commission. Edison relies upon the "publishers' exclusion" from the definition of investment adviser under Section 202(a) (11) of the Investment Advisers Act of 1940 and corresponding state securities laws. This report is a bona fide publication of general and regular circulation offering impersonal investment-related advice, not tailored to a specific investment portfolio or the needs of current and/or prospective subscribers. As such, Edison does not offer or provide personal advice and the research provided is for informational purposes only. No mention of a particular security in this report constitutes a recommendation to buy, sell or hold that or any security, or that any particular security, portfolio of securities, transaction or investment strategy is suitable for any specific person.

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1,185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia