Utilising the UK CF Registry to support reimbursement decision-making

Principles of managed access to new cystic fibrosis therapies

Introduction

Around 10,500 people live with cystic fibrosis in the UK. It is a life-limiting, inherited disease.

Disease-modifying cystic fibrosis therapies are being developed for greater numbers of people with the condition. Vertex Pharmaceuticals Inc. have licensed two such medicines for use in Europe: ivacaftor monotherapy (Kalydeco®) and lumacaftor/ivacaftor combination therapy (Orkambi®).

Kalydeco® is prescribed through the NHS in the UK for around 410 eligible patients with indicated cystic fibrosis-causing genetic mutations. Orkambi's® license indicates that over 3000 people with cystic fibrosis in the UK could receive the drug.

The UK Cystic Fibrosis Registry currently monitors the safety and efficacy of ivacaftor, compiling reports for the European Medicines Agency (EMA), as part of a scalable post-marketing surveillance programme that enables comparison of people on drug with their own legacy data in additional to a comparator cohort matched from the entire CF population.

The Cystic Fibrosis Trust proposes that data collected routinely by UK CF Registry is utilised to create an early access programme that supports the NHS to invest securely in controlled, early access to novel cystic fibrosis medicines.

Challenge

Well-powered and designed clinical trials have demonstrated a clinical benefit and good safety profile for both therapies. The key data used to describe efficacy were derived from two clinical endpoints:

1. Absolute increase in percentage predicted Forced Expiratory Volume in 1 second ($ppFEV_1$)
2. Rate of pulmonary exacerbations (PEx)

Whilst the Trust recognises the importance of these endpoints, there are four important limitations to the nature of the data captured in the clinical trials:

1. By virtue of targeting disease-modification, these treatments may have a protective impact on future health deterioration. Where the experience of Kalydeco® indicates a growing body of evidence that the therapy slows disease progression and facilitates compound health improvement – the evidence from the clinical trials and rollover studies to see if this effect is replicated or not in newly licensed therapies will be immature.

2. People affected by the condition experience the benefit and value of therapies in more dynamic and personally meaningful ways than the trial is designed to capture. Many current trials have captured QoL data limited to the CFQ-R respiratory domain.

3. Typical trial data, set to meet clinical and safety regulatory standards, make it difficult to holistically model the value of these medicines to the NHS and create an evidence gap in prescribing practice and clinical use. Tools such as the EQ5-D, benchmarking against ONS national well-being scores, and CF QoL measures, utilised in a setting with greater opportunity for longitudinal comparison, can develop our understanding of the less tangible value of new CF therapies.

4. As new treatments become available, the population of people with cystic fibrosis eligible to participate in a clinical trials may be less – increasing the likelihood of traditional clinical trial design having insufficient power to assess outcomes of upcoming therapies.

Is the UK CF Registry a key tool in a solution?

With near-complete coverage of the UK's cystic fibrosis population, the UK CF Registry is uniquely positioned to demonstrate the effect of new CF treatments in the real world, with enough patients and over a long enough time period for the impact of breakthrough therapies to be understood.

The UK Cystic Fibrosis Registry

The UK Cystic Fibrosis (CF) Registry is a national, centralised web-based database that collects demographic, health and treatment data from consenting people with cystic fibrosis from every CF care centre in England, Wales, Scotland and Northern Ireland. The UK CF Registry is sponsored and managed the Cystic Fibrosis Trust.

Over 99% of people with cystic fibrosis consent to their anonymised data being collected in the Registry, which utilises data for research, annual reporting, quality improvement, and as the evidence base for the cost of cystic fibrosis care, informing proportionate tariff payments by NHS England. It is also relied upon by the European Medicines Agency to evaluate the safety and efficacy of therapies for post-marketing surveillance.

The Cystic Fibrosis Trust has committed to extensively enhancing the UK CF Registry, migrating it to a new agile software system that can collect data for Registry-based clinical trials. It has been designed with capability to enable direct access to people with cystic fibrosis via a patient portal in future. This portal would enable people with cystic fibrosis to view their clinical data, self-report data, and opt in to additional uses of Registry data that will enhance the value of the Registry to the CF community.

The Cystic Fibrosis Trust

We are the UK's only national charity dealing with all aspects of cystic fibrosis. We fund research to improve cystic fibrosis care and treatment, and aim to ensure appropriate clinical care and support for people with cystic fibrosis.

In October 2015, the Trust devised and rolled out a survey that asked about the life experience and treatment preferences of people affected by cystic fibrosis. We received over 1400 responses from our community. Analysis showed that a treatment's potential to protect future health and wellbeing is more important than a treatment's potential to reduce symptoms in the short term. These data will be published once further data mining has taken place.

We are committed to representing this view in the way new therapies for cystic fibrosis are assessed.

Question

What data collection methodology, including choice of quality indicators and analysis period, is necessary for the NHS to confidently predict the long-term value, including health-related quality and length of life, of new cystic fibrosis therapies to the NHS?

Proposed mechanism for discussion

The Trust proposes that new cystic fibrosis medicines should be made available for specialist clinical prescription immediately following marketing authorisation in the European Union, on the condition that an agreed set of data are routinely monitored through UK CF Registry data against the therapies' performance at a population level.

We suggest the therapy should be concurrently evaluated by a UK-wide technology appraisal body, with three options available to the Appraisal Committee at the conclusion of the process:

1. Recommended for routine use and funded from the baseline commissioning budget (a drug which thus demonstrates both clinical and cost effectiveness).

2. Not recommended for routine use and thus there is no baseline funding (a drug which thus does not demonstrate clinical effectiveness).

3. Recommended for use for evaluation within a predetermined period of time (e.g. 12 months evaluation period plus 6 months for data collection and analysis) in order to build both an extended and novel evidence base via the UK CF Registry's patient records.

After this time, an abbreviated appraisal process would be undertaken to formally review the collated data, and issue final guidance regarding the therapy's continued use.

Next steps

We invite you to help us to better understand the suitability of (1) change in the rate of pulmonary exacerbations (represented by home/hospital IV episodes), (2) absolute change in $ppFEV_1$, (3) change in rate of decline in $ppFEV_1$, and (4) change in BMI, as the key outcomes that meaningfully represent therapeutic added value, in cystic fibrosis and can help to build a real-world picture of the impact of a therapy, through extended longitudinal data beyond clinical trials and rollover studies.

Alongside these metrics, we would like to discuss the added benefit to an NHS assessment of value of a new CF therapy of reporting UK CF Registry data to describe (5) use of services (represented by medications, airway clearance, supplementary feeding, IV days, non IV admissions, transplant), (6) health utility scores (represented by EQ5-D or other), and (7) personal independence scores (represented by CFQ-R).

The establishment of any proposed mechanism of novel cystic fibrosis therapy appraisal must be underpinned by an acceptable interim commercial access arrangement, which confirms the cost of the drug to the NHS (agreed between the company and the NHS) and data collection arrangements. However, we are concerned with the practical arrangements needed to collect high-quality, real world data, in order to facilitate such an arrangement.

We believe participation in the data collection exercise should be open to all eligible individuals covered by the EMA's marketing-authorisation guidance to enable assessment of impact at population level, and understand that participants must be informed and provide written consent in advance, agreeing to the time-limited nature of the data collection exercise.

We believe Orkambi® is a therapy where this pilot could be initiated with low administrative and infrastructural burden, as the necessary data collection already happens.

Data from the UK CF Registry could support such a pilot, running for a period of 12 to 24 months to provide sufficient time for the publication of the data from the data collection period.

We believe that the appropriate model could act as a more powerful rollover study that can call upon both cumulative data from the initial trials and historical data stored in the UK CF Registry, while boosting our holistic understanding of the therapy through collection of broader data points.