

Ivacaftor for cystic fibrosis

Protocol

1. Plain English Summary

Cystic Fibrosis (CF) is one of the most common, inherited diseases in white populations. Around 1 in every 2500 babies born in the UK has CF and there are over 9000 people in the UK with CF. CF is caused by a single faulty gene which controls the movement of salt and water in and out of cells. This results in thick sticky mucous clogging up the internal organs (e.g. lungs, pancreas, liver, intestine and reproductive tract) making it difficult to breathe and digest food. Other symptoms can include a troublesome cough, prolonged diarrhoea and poor weight gain. Most of the illness caused by CF is from diseases of the lungs and repeated infections. There is no cure for CF and most treatments (e.g. physiotherapy, antibiotics for infections, drugs to suppress inflammation) target the symptoms rather than the cause of disease. Median survival of the current UK cohort with CF is estimated as 41 years. Most patients die from lung disease. Life expectancy is increasing and is expected to increase to at least 50 years for children born in 2000.

A large number of different mutations have been identified in the gene that causes CF. New treatments are being developed which target specific mutations. Ivacaftor (brand name Kalydeco, Vertex Pharmaceuticals) is the first of these drugs and targets patients with the "G551D" mutation. Around 4.4% of patients with CF in the UK will have at least one G551D mutation. Ivacaftor represents a new approach to treating patients with CF as it targets the underlying cause of CF. It aims to increase salt movement through the cell by targeting a specific protein. Ivacaftor is classed as an "orphan drug" which means that has been developed specifically to treat a rare disease. It has been approved by the American Food and Drug Administration for the treatment of patients with CF who are at least 6 years old and have the G551D mutation. There are currently no similar drugs which target the underlying protein defect in CF on the market.

This review aims to evaluate the effectiveness of ivacaftor tablets for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have at least one *G551D* mutation. The review will consider both clinical effectiveness (improvement in patients' symptoms and adverse events) and cost effectiveness (cost of treatment).

2. Decision problem

2.1 Objectives

This review aims to appraise the clinical and cost effectiveness of ivacaftor 150mg tablet for oral administration for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have at least one *G551D* mutation in the *CFTR* gene. We will aim to determine the category of patients most likely to benefit from Ivacaftor by assessing whether the effects vary according to disease severity and age.

2.2 Background

Cystic Fibrosis is the most common, life-threatening, autosomal recessive disorder in Caucasian populations; it has an estimated carrier rate of 1 in 25 and incidence of 1 in 2500 live births.¹ It affects around 9000 people in the UK with a prevalence of 1.37/10 000.² CF was first recognised as a distinct disease in 1938.³ It is characterised by abnormal transport of chloride and sodium, leading to thick viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract and to an increased salt content in sweat gland secretions.⁴ Most of the morbidity and mortality is from pulmonary disease, which is characterised by bronchial and bronchiolar obstruction with thick tenacious secretions that are difficult to clear, colonisation by pathogenic bacteria and repeated infections.¹ There is chronic inflammation and progressive lung destruction can lead to bronchiectasis, altered pulmonary function, and respiratory failure. CF can also lead to CF related diabetes (CFRD), male infertility and liver involvement. In addition to repeated chest infections, symptoms of CF can include a troublesome cough, prolonged diarrhoea and poor weight gain.¹ Most patients with CF eventually succumb to lung disease and survival of patients with CF is currently around 41 years, a considerably increase from around 6 months when the disease was first identified,⁴ and is expected to increase to at least 50 years for children born in 2000.²

CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene which was discovered in 1989.⁵ It sits on chromosome 7, is some 250 kB in length, and encodes a protein of 1 480 amino acids. This protein is a chloride channel present at the surface of epithelial cells in multiple organs and is responsible for aiding in the regulation of salt and water absorption and secretion. Over 1000 disease-causing alleles within this gene have been identified although only 23 have been demonstrated to cause sufficient loss of CFTR function to confer CF disease.⁶ The most common mutation is the F508 mutation which is present on around 67% of CF chromosomes worldwide.⁷ The G551D (Glycine to Aspartate change in nucleotide 1784 in exon 11), which affects approximately 4.4% of patients with CF in the UK,⁸ is of interest as a new treatment has been developed targeted specifically at patients with this mutation. CFTR protein channels with the G551D mutation have a greatly reduced fraction of time that the channel spends in the open state, or “open probability,” and, therefore, have limited chloride transport ability.

Diagnosis of CF and genetic testing

The gold standard for the diagnosis of CF is the sweat test.⁶ This tests for elevated levels of chloride in sweat with a diagnosis of CF being made at levels above 60mmol/L, and a possible diagnosis of CF at level above 30 mmol/L. New born screening tests have been introduced in many countries, and have been routine throughout the UK since October 2007.⁹ These involve a small sample of blood being taken (“heel prick test”) which is tested for high levels of immunoreactive trypsinogen (IRT). If an abnormal IRT value is identified, most new born screening programmes perform a combination of DNA testing to identify known CFTR mutations and repeat IRT testing.¹⁰ IRT testing alone has a sensitivity of 82-

100%, double IRT testing increases sensitivity to 89-100% and IRT and DNA testing has a sensitivity of 94-100%; specificity is >99% for all testing strategies.¹¹ In the UK screening programme, the initial DNA test involves testing for 4 mutations (F508, G551D, G542X and 621+1G>T), if only one CF mutation is detected then further DNA analysis based on 29 or 31 mutations is recommended. A range of commercial kits are available for diagnostic testing. The diagnosis is then confirmed using the sweat test.¹⁰

Treatment of CF

There is no cure for CF and current treatments target the complications rather than cause of the disease.⁴ Treatments can be broadly classified as nutritional repletion (e.g. pancreatic enzyme supplementation and nutritional supplementation), relief of airway obstruction (e.g. physiotherapy, drugs to improve sputum clearance, bronchodilators), treatment of airway infection (e.g. antibiotics), suppression of inflammation (e.g. steroids, high dose ibuprofen) and lung transplantation.⁴

Ivacaftor

Ivacaftor (brand name Kalydeco, Vertex Pharmaceuticals) is the first in a new class of drugs known as CFTR potentiators which represents a new therapeutic approach to the treatment of patients with CF by targeting the underlying protein defect of CF. The drug facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the G551D-CFTR protein.¹²

Ivacaftor is a designated orphan medicinal product.¹³ It has been approved by the FDA for the treatment of CF in patients aged 6 years or older who have a G551D mutation in the CFTR gene¹⁴ and is the subject of a European Union marketing authorisation application. No active comparator agents that target the underlying CFTR protein defect in CF disease exist.¹⁵

3. Report methods for synthesis of evidence of clinical effectiveness

We will conduct a systematic review of the evidence on the clinical effectiveness of ivacaftor 150mg tablet for oral administration for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have at least one *G551D* mutation in the *CFTR* gene. The review will follow the general principles recommended in the PRISMA statement and CRD report 4.^{16, 17}

3.1 Search strategy

Literature searches will be undertaken in several stages to identify relevant information, such as eligible studies, evidence-based health technology assessments (HTAs), systematic reviews, economic evaluations, guidelines and health-related quality of life data. The EMBASE strategies will be independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.¹⁸

Clinical effectiveness

Searches will be undertaken to locate randomised controlled trials using ivacaftor. They will not be limited by date, language or publication status (unpublished or published). The following databases will be searched:

- MEDLINE (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP)
- EMBASE (OvidSP)
- Latin American and Caribbean Health Sciences Literature (LILACS) (VHL)

- <http://lilacs.bvsalud.org/en/>
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (Wiley & CRD)
- NHS Economic Evaluation Database (NHS EED) (Wiley & CRD)
- Health Technology Assessment Database (HTA) (Wiley & CRD)

Supplementary searches will be undertaken on the following resources to identify unpublished and on-going studies:

- metaRegister of Controlled Trials (Internet)
<http://www.controlled-trials.com>
- NIH Clinicaltrials.gov (Internet)
<http://www.clinicaltrials.gov>
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet)
<http://www.who.int/ictip/en/>

Scanning abstracts and programmes of relevant conferences will enable identification of relevant studies and projects. The following conference proceedings will be searched from 2007-2012:

- European Cystic Fibrosis Society (ECFS) conference
<http://www.ecfs.eu/conferences/main>
- North American Cystic Fibrosis Conference (NACFC)
<https://www.nacfconference.org/>
- International Congress on Pediatric Pulmonology (CIPP)
<http://www.cipp-meeting.org/index.htm>

The bibliographies of retrieved articles and relevant systematic reviews will be checked for additional studies. Identified references will be downloaded into Endnote bibliographic management software for further assessment and handling.

3.2 Inclusion criteria

Studies that fulfil the following criteria will be eligible for inclusion:

Population: Children (6 years and older) and adults with cystic fibrosis who have the *G551D* mutation on at least one *CFTR* allele. Patients with all severities of disease will be eligible.

Intervention: Ivacaftor tablets

Comparator: Any reported comparator

Outcomes: The primary outcome will be lung function (e.g. percent predicted forced expiratory volume in one second (FEV₁)). Other eligible outcomes include mortality, weight, BMI, sweat chloride, respiratory symptoms, reduction in pulmonary exacerbations, exercise tolerance, adverse effects of treatment, health-related quality of life and utilisation of hospital resources. Studies that only report short-term outcomes (<3 months only) will be excluded.

Study design: For the review of clinical effectiveness, only RCTs will be included. Criteria will be relaxed for consideration of adverse events, for which open label studies will be eligible.

The results of the searches will be screened for relevance independently by two reviewers. Full text of studies identified as potentially relevant will be obtained and assessed for inclusion by one reviewer and checked by a second. Disagreements will be resolved through discussion or referral to a third reviewer where necessary.

3.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form and checked by another. Disagreements will be resolved through discussion or referral to a third reviewer where necessary. Data will be extracted on the primary outcome, lung function (e.g. percent predicted forced expiratory volume in one second (FEV₁)), and the following additional outcomes: mortality, weight, BMI, sweat chloride, respiratory symptoms, reduction in pulmonary exacerbations, exercise tolerance, adverse effects of treatment, health-related quality of life and utilisation of hospital resources. Data will be extracted after 24 weeks (intermediate) treatment and after the longest duration of follow-up reported. If data are available for different patient subgroups (e.g. age, disease severity, region) then data will be extracted separately for each subgroup. If composite end points are reported, data will be extracted on the definition of the end point, results, and, if sufficient data are available, the events that contributed to the end point.

3.4 Quality assessment strategy

Trials will be assessed for methodological quality using the Cochrane Risk of Bias tool.¹⁹ This includes items covering selection bias (random sequence generation and allocation concealment), performance bias (participant blinding), detection bias (blinding of outcome assessors) attrition bias (incomplete outcome data), and reporting bias (selective reported). There is also an addition field for other sources of bias. We believe that all important concerns about bias are include in the other domains in the tool and so no further domains will be added. Each domain is assigned a rating of high, low, or unclear. Each trial will be assigned an overall rating of the risk of bias. If at least one of the domains is rated as “high” the trial will be considered at high risk of bias, if all domains are judged as “low” the trial will considered at low risk of bias, otherwise the trial will be considered at “unclear” risk of bias. The risk of bias assessment will be incorporated into the data extraction form and will be conducted as part of the data extraction.

3.5 Methods of analysis/synthesis

We do not anticipate having sufficient data to conduct a formal meta-analysis. Data will be tabulated and discussed in a narrative review. Details of the components of best supportive care, where reported in the included studies, will be clearly described. If sufficient data are available results will be grouped by age, lung function, disease severity, and prior treatment (including consideration of intolerance to treatments). Dichotomous data will be summarised as relative risks or hazard ratios together with 95% confidence intervals (CIs). Continuous outcomes will be summarised as mean differences between treatment groups together with 95% CIs; where appropriate mean differences between groups in mean change from baseline will be calculated. If sufficient data are available, results will be displayed graphically using forest plots. Publication bias will not be formally assessed as we only expect to include a very small number of trials. Standard methods to detect publication bias will therefore not be possible.

4. Report methods for synthesising evidence of cost-effectiveness

4.1 Identifying and reviewing published cost-effectiveness studies

Focussed searches will be undertaken to identify literature on cost-effectiveness and cystic fibrosis. Searches will be limited to the last ten years. The following resources will be searched:

- Medline (OvidSP)
- Medline In-Process Citations (OvidSP)

- Embase (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (CRD)
- Health Economic Evaluation Database (HEED)

Health-related Quality of Life

Focussed searches will be undertaken to identify literature on HRQoL and cystic fibrosis.

Searches will not be limited by date and the following resources will be searched:

- Medline (OvidSP)
- Medline In-Process Citations & Other Non-Indexed Citations (OvidSP)
- Embase (OvidSP)
- CEA Registry (Internet)

Guidelines and guidance

The following resources will be searched for guidelines and guidance related to cystic fibrosis:

- NICE Guidance (Internet)
<http://guidance.nice.org.uk/>
- TRIP database (limited to guidelines) (Internet)
<http://www.tripdatabase.com/>
- Guidelines International Network (GIN) (Internet)
- National Guidelines Clearinghouse (Internet)
<http://www.guidelines.gov>
- Cystic Fibrosis Trust
<http://www.cftrust.org.uk/>

Searches will focus on original papers that report on cost, cost-effectiveness or cost-utility analyses, either studying the diagnostic phase (genetic testing for CF mutations), therapeutic phase (management of patients with confirmed CF), or a combination. Note that this search does not only include studies on ivacaftor, but evaluations of any treatment for CF. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Data extraction will focus on interventions compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), for example relating to extrapolation of study results, analytical methods and robustness of the study findings.

4.2 Evaluation of cost-effectiveness

If an economic evaluation is provided by the manufacturer it will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used

in the economic model. If the team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a de novo model. Such de novo economic evaluation will be undertaken from a NHS and social care perspective. The model will draw together evidence from literature and study reports concerning treatment efficacy, withdrawal, treatment related adverse events, relevant diagnostic interventions, chronic care costs, and HRQoL. The model structure will be developed such that the effects of treatment on lung function, exacerbations, quality of life and treatment costs can be incorporated. The level of detail will depend on available evidence. Specifically, the impact of treatment on resource use in pulmonary exacerbations in both the primary and secondary care settings will be taken into account if data allows. If evidence allows, subgroups by age, lung function, disease severity, and prior treatment (including consideration of intolerance to treatments) may be considered. Additionally, the impact of treatment on resource use in pulmonary exacerbations in both the primary and secondary care settings will be taken into account if data allows.

Costs will be identified through literature searches. As genetic testing is essential to the use of ivacaftor it will be part of the assessment. If possible with the data available, the assessment of ivacaftor will consider the impact of treatment on progression through treatment bands over time, and take in to account any service implications (e.g. changes in type/duration/frequency of hospital activity). In line with current recommendations, costs and health outcomes will be discounted at 3.5%. Key health economic outcomes are likely to include the cost per life year gained, and the cost per quality adjusted life year (QALY) gained. The cost-effectiveness of interventions will be compared incrementally against each other. Sensitivity analysis will be undertaken to examine the key determinants of cost-effectiveness. Probabilistic sensitivity analysis (PSA) will be undertaken to generate information on the likelihood that each treatment produces the greatest amount of net benefit. The results of this PSA will be presented as cost-effectiveness acceptability curves (CEACs).

5. Timetable/milestones

Milestone	Deadline
Protocol Submitted	22 May
Searches	10 May
Reference Screening	10 May
Inclusion assessment	14 May
Data extraction and quality assessment	24 May
SR results section draft	24 May
Health economic results to KSR	29 June
Health economics section complete	6 July
Report to commissioner	10 July
Comments from Commissioner	31 July
Final report	17 August

6. Team members' contributions

Penny Whiting will be the main reviewer on this project and will maintain day-to-day running of the review. Marie Westwood will act as second reviewer. Both reviewers have contributed to the study protocol and will carry out the study selection, data extraction, analysis and production of the final report. Maiwenn Al will be health economic lead for this project, and thus be responsible for the cost-effectiveness study.

7. References

- [1] Cystic Fibrosis Trust. *Standards for the clinical care of children and adults with cystic fibrosis in the UK [Internet]*. 2nd ed. London: Cystic Fibrosis Trust, December 2011 [cited 7.5.12]. Available from: http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/CF_Trust_Standards_of_Care_2011_%28website_Apr_12%29.pdf
- [2] Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. *Eur Respir J* 2007;29(3):522-6.
- [3] Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease. *Am J Dis Child* 1938;56(2):344-99.
- [4] Davis PB. Cystic fibrosis since 1938. *Am J Respir Crit Care Med* 2006;173(5):475-82.
- [5] Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989;245(4922):1073-80.
- [6] Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 2008;153(2):S4-14.
- [7] Correlation between genotype and phenotype in patients with cystic fibrosis. The Cystic Fibrosis Genotype-Phenotype Consortium. *N Engl J Med* 1993;329(18):1308-13.
- [8] UK CF Registry [Internet]. Bromley, Kent: Cystic Fibrosis Trust, 2011 [cited 12.6.12] Available from: <http://www.cftrust.org.uk/aboutcf/publications/cfregistryreports/>
- [9] The UK NSC policy on cystic fibrosis screening in newborns [Internet]. London: UK Screening Portal, 2012 [cited 8.5.12] Available from: <http://www.screening.nhs.uk/cysticfibrosis-newborn>
- [10] UK Newborn Screening Programme Centre. *Figure 1. CF screening flow chart. In: A laboratory guide to newborn screening in the UK for cystic fibrosis (3rd edition) [Internet]*. London: UK Newborn Screening Programme Centre, 2009 [cited 8.5.12] Available from: <http://newbornbloodspot.screening.nhs.uk/getdata.php?id=10967>
- [11] Serra-Prat M. *Neonatal screening for cystic fibrosis. BR01/2000 [Internet]*. Barcelona: Catalan Agency for Health Technology Assessment (CAHTA), 2000 [cited 8.5.12] Available from: <http://www.gencat.cat/salut/depsan/units/aatrm/pdf/br0001en.pdf>
- [12] Davis PB, Yasothan U, Kirkpatrick P. Ivacaftor. *Nat Rev Drug Discov* 2012;11(5):349-50.

- [13] European Medicines Agency. *Orphan designation [Internet]*. London: European Medicines Agency, 2012 [cited 8.5.12] Available from: http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce
- [14] U.S. Food and Drug Administration (FDA). *FDA approves Kalydeco to treat rare form of cystic fibrosis. FDA news release [Internet]*. Silver Spring, USA: FDA, 2012 [cited 8.5.12] Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=Kalydeco&utm_content=1
- [15] Vertex Pharmaceuticals Inc. *Ivacaftor for the management of cystic fibrosis. Formulary submission dossier*. Cambridge, USA: Vertex Pharmaceuticals Inc, February 2012.
- [16] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151(4):264-9.
- [17] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [cited 23.03.11] Available from: <http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm>
- [18] McGowan J, Sampson M, Lefebvre C. An evidence based checklist for the peer review of electronic search strategies (PRESS EBC). *Evidence Based Library and Information Practice* 2010;5(1):1-6.
- [19] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

Appendix: Draft search strategy

EMBASE (OvidSP): 1974-2012/wk17

Searched 3.5.12

- 1 Ivacaftor/ (72)
- 2 (Ivacaftor or Kalydeco or VX-770 or VX770 or 873054-44-5 or ivacaftorum).af. (138)
- 3 or/1-2 (138)