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Dear CHMP Chair and Vice-Chair,

We are writing on behalf of our two organisations, the European Cystic Fibrosis Society (ECFS) and Cystic Fibrosis Europe (CFE), a patient-representative organization with members from 39 countries. We individually contacted you in 2024 regarding the license extension being considered for kaftrio® (elexacaftor/tezacaftor/ivacaftor, ETI). Ahead of the CHMP vote at the end of February, we are writing again, both to highlight new data and to emphasise the importance we jointly attach to the issue. The decision being considered has major consequences for the future health and wellbeing of our CF patient community.

As you are aware, cystic fibrosis is caused by variants in the *CFTR* gene. From the time of diagnosis, treatment burden is high, impacting quality of life and life choices; most people with CF ultimately develop respiratory failure leading to a reduced life expectancy. CFTR modulators, which can restore function of the defective protein in the majority of cases have become standard of care; the most recent of these, kaftrio®, has been transformative, in terms of both physical and psychological health for those who can access the therapy.

The combination of molecules in kaftrio (elexacaftor, tezacaftor, ivacaftor; ETI) was developed and selected for clinical progression based initially on laboratory testing of the most common CFTR variant *F508del*. Two phase 3 trials included people with either one or two copies of *F508del* and led to the licensing of the drug based on a highly impressive efficacy signal (lung function, pulmonary exacerbation/ hospitalization rates and validated quality of life assessment) combined with good safety. Initial licenses (FDA 2019 and EMA 2020) gave thousands of people with cystic fibrosis bearing *F508del* access to this treatment. Real-world reports are unanimous in confirming clinical trial data: the course of the disease improves dramatically on kaftrio® with a rapid, major and sustained improvement in clinical manifestations and lung function, strongly predicted to result in longer survival.

Although CF is a monogenic disorder, ETI will not work for all patients; this unusual situation relates to the fact that over 2,000 different variants (mutations) have been reported in the *CFTR* gene. A minority of these lead to an absence of CFTR protein, and thus, no substrate upon which modulator drugs can work.

In contrast, **the majority of mutations, many of which are ultra-rare, lead to a CFTR protein with abnormal structure or function**. The large number of these variants, coupled with the rarity of each one, means it is impossible to conduct clinical trials fulfilling all the requirements of clinical research for each of them. In this context, over the last few years, both industry and clinical academia have strived to generate data on these rarer mutations. From several different approaches, an evidence base is growing that many other variants, most of them rare, are also 'responsive'.

Modulator drugs were initially developed and refined through a screening system on Fisher rat thyroid (FRT) cells, which were specifically engineered to express various forms of mutated CFTR. Based on FRT data provided by Vertex, the drug manufacturer, the FDA has twice expanded its license for ETI (Trikafta), including a further 177 variants in 2020 and another 94 in Dec 2024. Perhaps unsurprisingly for such a novel approach, questions were initially raised about the suitability of FRT in predicting drug responsiveness, leading until now, to a lack of acceptance of such data by EMA. We consider that the evidence base is growing, alongside several other lines of evidence to support clinical suitability of Kaftrio for patients with many other CFTR variants. We are aware you have been provided with this evidence, but thought our societies' combined reflections and interpretations may add value to your committee's considerations.

The initial 177 FDA license expansion allowed access for an additional 5.2% of people on the CF Foundation's patient registry who became newly eligible for treatment. A recently published registry study[1] assessed clinical outcomes in this group. ETI treatment was associated with robust improvements in FEV1 and pulmonary exacerbation rate which were of a greater magnitude in people naïve to previous modulator use (eg. ivacaftor or tezacaftor/ iva).

Retrospective registry data do have limitations. Prospective studies from the *French Compassionate Programme* provides complementary and highly supportive data. The French CF Society (Vaincre la Mucoviscidose) and Patient Organisation collaborated on a programme to expand access for their patients with rare mutations, originally through a compassionate use project for severely sick patients[2], and later expanded to all patients except those with two mutations known to be non-responsive (no CFTR protein made)[3]. Their two papers published to date demonstrate that of 443 modulator-naïve people:

- 83 had **at least one** FDA-approved variant; 81 (98%) of these were demonstrated 'responsive' on the basis of changes in FEV1 and/ or sweat chloride. Group changes were substantial and mirrored those seen in clinical trials.
- 360 participants **had no** FDA-approved (at the time) variant. 49% of them were also ETI responders demonstrating similarly large group changes.

The French reimbursement system allows ongoing access for these people.

A randomized, controlled clinical trial conducted by Vertex and presented at ECFS conference 2024 (as yet unpublished) also provided evidence of a robust clinical response (FEV1 and sweat chloride) in people harbouring a number of FRT-responsive, non-F508del variants. Smaller case reports and case series have used a variety of approaches including organoid responsiveness and n-of-1 clinical testing approaches to assess responsiveness of rare mutations, which in some regions have allowed access for patients.

The international guidelines for standards of care published recently by the ECFS in the *Journal of Cystic Fibrosis*[4] recommend that people with cystic fibrosis **and at least one responsive non-*F508del* variant should be considered for treatment** with CFTR modulators. Equal access to medicines for patients in all European member States is one of the pillars of the Pharmaceutical Strategy for Europe, with a special focus on rare diseases. However, at present, there is inequity of access to kaftrio® across Europe. Depending on the country they live in, some patients with a non-*F508del* modulator-responsive variant may have access to kaftrio®; in other regions access is currently not possible.

Therefore, on behalf of the European Cystic Fibrosis Society (ECFS) and CF Europe we wish to express our full support for an extension of approval for elexacaftor/tezacaftor/ivacaftor (kaftrio®) in combination with ivacaftor. We believe that in addition to data from clinical trials, data from *in vitro* experiments and real-world evidence should be considered as strong evidence of kaftrio® effectiveness. Moreover, as kaftrio® is truly a transformative drug for the very severe disease that is cystic fibrosis, and is largely safe, we advocate for an approval of ETI (kaftrio®) in combination with ivacaftor for **all people with cystic fibrosis who bear at least one responsive non-*F508del* variant.** In certain cases, prior evidence of such responsiveness may be lacking and may be obtained through clinical assessment of the pwCF before and after a short course (eg. 4 weeks) of ETI therapy. As a community we have developed multiple ways to demonstrate such 'responsiveness', including cell-based, tissue/ organoid based and well-validated clinical assessments. Much data exists already for many of these variants, whilst people harbouring these are experiencing declining health and well-being, in stark contrast to their counterparts in other regions. We are encouraged that EMA is considering expanding the license for ETI and very much hope that this exercise will have a positive outcome, with allowance for **all forms of evidence to be considered alongside expert clinical judgement**.

Yours sincerely,

Jane Davies OBE, FMedSci, FRCPCH, on behalf of the European CF Society

Thierry Nouvel, on behalf of CF Europe

1. Eur Respir J. 2024 Nov 14;64(5):2401146.
2. Eur Respir J. 2023 May 5;61(5):2202437.
3. Lancet Respir Med. 2024 Nov;12(11):888-900.
4. Journal of Cystic Fibrosis, Volume 22, Issue 1, 17 - 30