Cystic Fibrosis Europe
J. Borlélaan 12, BE 1160 Brussels
+32 (0)2/61 32 716
www.cf-europe.eu

Dr Harald Enzmann
Chair – Committee for Medicinal Products for Human Use (CHMP)
c/o European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

19th May 2020

For the attention of the CHMP Chair and the Rapporteurs for elexacaftor–tezacaftor–ivacaftor triple combination therapy for the treatment of cystic fibrosis

Dear Dr Enzmann,

I write on behalf of CF Europe, the federation of 48 national cystic fibrosis (CF) Associations, representing people with CF and their families in 39 countries.

In our February correspondence, we appealed to the CHMP to review the latest triple combination modulator therapy, elexacaftor–tezacaftor–ivacaftor, with a sense of urgency. Today, the urgent need for this therapy could not be greater. We request that the CHMP consider a conditional marketing authorisation for this therapy. In addition, we request your opinion on compassionate use access for the therapy in Europe.

We would first like to extend our sincere thanks to the European Medicines Agency (EMA) for their role in providing the European CF community with access to transformational CFTR modulator therapies in recent years. Around half of the CF population are now eligible for authorised modulator therapies, which are projected to extend the lives of thousands[1,2].

In recent months, we have seen unprecedented pressures placed on our healthcare systems, as countries across Europe respond to the challenges of the COVID-19 pandemic. The threat of viral respiratory tract infections is particularly profound for people with CF, as they carry an increased risk of complications and irreversible lung damage[3]. Early reports suggest that government 'shielding' measures and entrenched protective habits within the CF community have been successful so far in limiting the incidence of COVID-19 within the European CF community[4], though figures are worryingly increasing[5] and people living with CF remain very vulnerable after lockdown.

Prioritisation of healthcare resources and staffing towards COVID-19 has altered how many services are being delivered. According to a recent *Rare Barometer* survey launched in collaboration with EURORDIS, reaching 768 people amongst the CF community across 31 countries, these changes are creating challenges in meeting standards of care, including those of the European Cystic Fibrosis Society (ECFS)[6]. A majority of CF patients reported delays or

[1] Rubin, J.L et al. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. *Therapeutic advances in respiratory disease*. 2019
[2] Burgel, P.R et al. Real-life safety and effectiveness of lumacaftor–ivacaftor in patients with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine*. 2020.
[3] Colombo, C et al. Impact of COVID-19 on people with cystic fibrosis. *The Lancet Respiratory Medicine*. 2020
[4] Cosgriff, R et al. A multinational report to characterise SARS-CoV-2 infection in people with cystic fibrosis. *Journal of Cystic Fibrosis*. 2020
[5] https://www.ecfs.eu/covid-cf-project-europe
[6] Castellani, C et al. ECFS best practice guidelines: the 2018 revision. *Journal of cystic fibrosis*. 2018

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cancellations due to COVID-19 to rehabilitation therapies (78%), routine appointments (72%), diagnosis laboratory tests (67%) and surgery and transplant (49%), risking unnecessary mortality and morbidity. Many families have been discouraged to go to the hospital and guided towards home self-care with 65% of patients using teleconsultations whilst only 21% have received appropriate training and education to manage the disease themselves.

In addition, much of the clinical trial research for CF therapies has come to a stand-still, with no new trials being initiated or recruitment to ongoing trials suspended[2,7]. This means potential trial participants are now locked out of receiving life-saving therapies through the clinical trial route.

One group with a desperate need for access to life-saving treatments is people awaiting a lung transplant. As outlined by the Global Transplantation Covid Report, due to resource diversion and the risk of invasive surgeries and immunosuppression, transplant activity has been functionally paused[8,9]. For many people with CF awaiting a transplant, progressive lung damage will mean, when transplant activity restarts, they will be too unwell to survive the surgery. Pneumologists have also reported globally that requisition of critical care beds has drastically decreased the number of donors.

As we each navigate this global health crisis, there is a critical need to explore every option available to protect the most vulnerable from this virus. There is an opportunity for the EMA to take a leading role in supporting people with CF across Europe, through expediting market authorisation to elexacaftor–tezacaftor–ivacaftor via a conditional marketing authorisation. Clinical trial evidence for the therapy has demonstrated a high safety and efficacy profile in all the mutation combinations studied[10,11]. The strong probability that a single Phe508del allele is sufficient to impart the benefits of this therapy outweighs the uncertainties during these exceptional circumstances. We urge the CHMP to propose discussions with the applicant on granting a conditional market authorisation for all patient with at least one Phe508del mutation in anticipation of forthcoming clinical trial data of additional mutation combinations[12]. We CF Europe, in collaboration with the ECFS and the European Patient Registry, commit to provide real world clinical data and patient-reported outcome measures to strengthen the dossier and document the effect of the drug on rare untested mutations.

In further response to these exceptional circumstances, and pending reimbursement agreements at the national level for the CF community, we would like to request a CHMP opinion on compassionate use access to the therapy. Though requesting an opinion is typically reserved for member states of the European Union, Article 83 of the EMA regulatory framework does not explicitly exclude patient organisations from also requesting an opinion on compassionate use. In some countries, compassionate use schemes have supported people in the most critical conditions, allowing access to elexacaftor–tezacaftor–ivacaftor as a bridging therapy to transplant. However, across different countries there is varying access to this programme, and the criteria to access the therapy also differ. We request the CHMP recommend a common set

[7] Vertex Pharmaceuticals. 2020. Vertex Confirms Supply Chain Continuity And Business Outlook For Its Cystic Fibrosis Medicines And Provides Initial Update On Development Programs. [online] Available at: https://investors.vrtx.com/news-releases/news-release-details/vertex-confirms-supply-chain-continuity-and-business-outlook-its [Accessed 1 May 2020].
[8] Lei, S et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EclinicalMedicine (Published by the Lancet)*. 2020
[9] Ahn, C et al. Global Transplantation COVID Report March 2020. *Transplantation*. 2020
[10] Middleton, P et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *New England Journal of Medicine*. 2019
[11] Heijerman, HG et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet*. 2019
[12] ClinicalTrials.gov. 2020. A Phase 3 Study of VX-445 Combination Therapy in Cystic Fibrosis (CF) Subjects Heterozygous for F508del and a Gating or Residual Function Mutation (F/G and F/RF Genotypes). Available at: https://clinicaltrials.gov/ct2/show/NCT04058353 [Accessed 12 May 2020]

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of conditions, under which emergency access to the triple combination therapy is made available through compassionate use for the people most at risk. This will allow member states to support people with CF in their country, as well as expanding compassionate use to countries who have previously not had the opportunity to provide this form of emergency access to patients with an acute need.

In addition to this letter, we are in communication with Vertex Pharmaceuticals and national authorities of our member organisations, reiterating this sense of urgency and need for goodwill from all stakeholders, to expediate access to the triple combination therapy for our CF community.

Once again, we extend to you our support, including the valuable expertise of people with CF and their families, and specialist clinicians and researchers from across Europe. As a federation, we are available to provide further evidence and insights from our communities if this would support your work, and discuss, for example, the feasibility of post-marketing research, should a conditional authorisation be granted. Ongoing work by CF Europe and our member organisations is on hand to support the CHMP in during this process.

Yours sincerely

Jacquelien J Noordhoek MA MSc
President CF Europe