Cystic Fibrosis Europe
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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

6 February 2020

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

Dear Dr Enzmann

I write on behalf of CF Europe, the federation of 48 national CF Associations in Europe, representing people with CF and their families in Europe.

The cystic fibrosis (CF) community worldwide welcomed publication of data on the triple combination treatment, Elexacaftor with Tezacaftor and Ivacaftor, as seminally positive progress in a broader mission to beat cystic fibrosis disease.

The results from the two pivotal phase III studies of the combination regimen show improvements of an unprecedented magnitude in the target population. It is clear the clinical benefit of the triple combination therapy goes beyond previously licenced combination therapies in its efficacy. Ivacaftor monotherapy has been considered the benchmark for a highly effective modulator therapy for individuals with at least one 'gating' mutation. Such mutations are present in about 5% of the CF patient population worldwide and in the EU.

Evidence from the triple combination clinical trials show equivalent levels of improvement are possible for a much more common mutation. The significance of this is more than 80% of the European CF community have a genotype amenable to treatment with a life-changing, highly effective modulator therapy.

For the European CF community, the treatment's anticipated licensing by the European Medicines Agency (EMA) later this year, is recognised as the next major milestone in the path towards enabling the majority of people with CF the opportunity to benefit from this highly effective new therapy.

In times of globalised social media, the testimony of people with CF already receiving the treatment has reached far and wide and there is heightened expectation and anticipation.

Naturally, people with CF who may benefit and their families are anxious to have the opportunity to try the treatment and - in the context of the progressive nature of their condition and their severe unmet need - find waiting for necessary processes to conclude agonising and stressful.

We are, therefore, grateful for the Agency's decision to review the treatment under Accelerated Assessment procedures.

The urgency of providing access to this treatment is difficult to overstate. Case reports already suggest that the treatment can substantially improve the health and quality of life of people experiencing end-stage CF disease. This acute benefit, demonstrated in a relatively healthier population in the Phase III trials, is in addition to the reduction in

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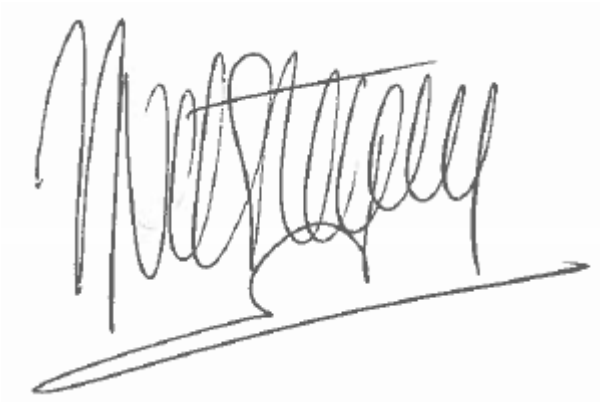
health events linked to disease progression observed in the trials. Avoidance of such events may translate into cumulative benefit for many years to come and echoes the effects seen with ivacaftor monotherapy. Longitudinal clinical and real-world registry data show the sustained benefits ivacaftor therapy has had on its eligible population, from increasing lung function and reducing infections, to nutritional benefits that help people with CF to live longer, healthier lives. There is now considerable promise that the triple combination therapy will expand these life-changing effects to a much larger population in the CF community.

While some clinical studies are still underway for this therapy, it is generally accepted that it is not feasible with currently validated technologies and procedures to thoroughly test the clinical response of all mutation combinations. We are concerned that people with CF whose cystic fibrosis transmembrane regulator (CFTR) gene mutation pairing includes Phe508del and a rare mutation for which clinical trial data are not currently available will be excluded from the eventual therapeutic indication of the Marketing Authorisation currently under review.

We ask, in this context, that due consideration is given to ensuring that the therapeutic indication does not inadvertently exclude individuals who can expect to benefit from the treatment through highly effective modulation of their single Phe508del mutation, as a consequence of having a rare second allele mutation. The current clinical trial data for the triple combination suggests there is strong support for the hypothesis that presence of a single Phe508del allele is sufficient to impart the benefits of this therapy. We therefore strongly believe that a European licence for this therapy should reflect this sentiment. We would be grateful if you would describe your approach to this challenge.

We would like to extend to you an offer of our community's support, including the expertise of people with cystic fibrosis and their families, and specialist clinicians and researchers from across Europe, and hope you will be able to utilise their important insights in your work and considerations.

Yours sincerely



Jacquelien J. Noordhoek MA MSc
President
CF Europe

Representing 48 national CF Associations, see next page.

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Member Organisations of CF Europe

CF Clearly Future (Austria)

Cyst. Fibrose Hilfe Österreich

CF Hilfe OÖ

CF-Hilfe Wien

Muco vzm (Belgium)

CF Bosnia

CF Bulgaria

CF Croatia

Czech Cystic Fibrosis Association

Cystisk Fibrose Foreningen (Denmark)

Estonian CF Society

Suomen CF-yhdistys/ CF Association in Finland

Vaincre la Mucoviscidose (France)

Mukoviszidose e.V. (Germany)

Deutsche CF-Hilfe

Association for Cystic Fibrosis (Greece)

Helenic Cystic Fibrosis Association

Országos Cisztás Fibrózis Egyesület

Cystic Fibrosis Association of Ireland

Cystic Fibrosis Fundation of Israel

Associazione Campana ONLUS (Italy)

Lega Italiana Fibrosi Cistica Onlus

Association for persons with Cystic Fibrosis (Kosovo)

CF Association of Latvia

Lithuanian Cystic Fibrosis Asociacion

Association de Lutte contre la Mucoviscidose (Luxembourg)

Zdruzenie za Cisticna Fibroza (Macedonia)

National Association Fighting CF (Moldova)

Association for help and support for people with CF of Montenegro

Nederlandse Cystic Fibrosis Stichting

Norwegian CF association

Polish Society Against Cystic Fibrosis

Matio Foundation (Poland)

Associaçao Nacional de Fibrose Quística (Portugal)

Romanian CF Association

AAFC. Romania

Help to CF patients (Russia)

Help and support to people with CF (Serbia)

Slovak CF Association

Društvo za cistično fibrozo Slovenije

Federación Española de FQ

Swedish Cystic Fibrosis Association

Fonden Citronfjärilen (Sweden)

Cystic fibrosis association Switzerland

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