29th September 2023

Submission of comments on 'Reflection paper on establishing efficacy based on single-4 arm trials submitted as pivotal evidence in a marketing 5 authorisation' (EMA/CHMP/564424/2021)

Comments from:

Name of organisation or individual

European Cystic Fibrosis Society (ECFS)
The European Cystic Fibrosis Society is an international community of scientific and clinical professionals committed to improving survival and quality of life for people with CF by promoting high quality research, education and care. The following comments are provided by the ECFS Clinical Trials Network (ECFS-CTN) and Patient Registry (ECFSPR).

Cystic Fibrosis Foundation (CFF)
The US-based CF Foundation is engaged in virtually every element of the research and development process—from preclinical discovery and identification of new therapeutics to conducting clinical trials and post-marketing surveillance. Their research and investment portfolio includes CFTR modulators, symptomatic treatments, and a growing array of biologics, such as mRNA and gene therapies.

Cystic Fibrosis Europe
Cystic Fibrosis Europe (CFE) is the federation of national and regional CF Patient Organisations in Europe with members in over 39 countries. CFE promotes and supports patient-centred research, promotes the best care from the perspective of people with CF, represents and defends the interests of people with CF, informs member organisations and supports sharing of best practice.

About cystic fibrosis
Cystic fibrosis (CF) is a rare multiorgan condition caused by pathogenic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, and affects approximately 54,000 people throughout Europe.[1] CFTR modulator medicines, which target the defect caused by certain *CFTR* variants, have transformed the CF therapeutic landscape and improved the lives of those eligible for the therapy (approximately 90% of people with CF).

Despite these advances, new therapies and therefore clinical trials are still required, both for therapies targeting downstream effects and symptoms of CF and for innovative therapies treating people with CF

[1] 2021 Annual report, European Cystic Fibrosis Society Patient Registry

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with rare *CFTR* variants, who are ineligible for modulator therapy. A robust pipeline exists, with numerous innovative therapies including mRNA and gene therapies.[2]

Clinical trials to advance the CF pipeline are limited by a reduced potential pool of people with CF eligible to participate, based on key inclusion and exclusion criteria such as *CFTR* variant, active treatment status, and lung function. The widespread clinical use of CFTR modulators in many countries has effectively resulted in a new, ultra-orphan population consisting of people with CF who are either modulator-ineligible or -intolerant, or who are without CFTR modulator access.

It is becoming increasingly difficult to design adequately sized randomised clinical trials (RCTs) to evaluate new therapies in these restricted populations. Therefore clinical trial design in CF must evolve to meet these challenges.[3] The logistical difficulties of conducting CF clinical trials in a post-CFTR modulator era may be mitigated by alternative trial designs including single arm trials (SATs) with appropriate comparator external data, such as the real-world data collected by ECFSPR and other CF patient registries.

We appreciate the opportunity to contribute our comments to EMA regarding SAT design and conduct.

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

[2] https://apps.cff.org/trials/finder/
[3] Advancing the pipeline of cystic fibrosis clinical trials: a new roadmap with a global trial network perspective, Mayer-Hamblett et al, 2023 doi.org/10.1016/S2213-2600(23)00297-7

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The reflection paper accurately describes the limitations, potential biases and mitigations associated with single arm trials. However we believe that the paper doesn't address some difficult issues, discussed in the comments table below, such as: - when SATs are acceptable - establishing external control arms - assessing safety In addition, pivotal trials, including SATs, **must also provide acceptable evidence for downstream health technology assessment (HTA)**. This is particularly important for rare diseases, where clinical trial populations are limited. It is essential that EMA coordinates with HTA bodies throughout Europe to ensure that advice given to companies regarding the acceptability of SATs is in line with HTA evidence requirements. This will avoid research waste, and clinical trials that do not generate the evidence necessary to bring the medicine all the way into the hands of patients. We suggest that sponsors seeking advice on clinical development plans including a pivotal	

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	SAT automatically undergo parallel scientific consultation from EMA and the European Network for Health Technology Assessment (EUnetHTA) 21 consortium. This could be integrated with the existing route of parallel scientific scientific and protocol assistance from EMA and the FDA, to achieve global consensus on clinical trial design for ultra-rare populations.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
203-205 231-232 When is a SAT suitable?		Comment: The paper states that the decision to rely on a single arm trial lies with the sponsor, that the sponsor should seek scientific advice, and that decisions are made on a case by case basis. We believe that EMA must provide more extensive and specific guidance on how to determine when an SAT is necessary and appropriate. This is especially important to limit "creep" or generalised acceptance of single arm trials as providing sufficient evidence in other situations (such as label extensions into younger age groups).	
Lines 208-282 Endpoints		Comment: We note that the reflection paper does not mention the use of patient-reported outcome measures (PROMs). We support the inclusion of suitably validated PROMs to reflect changes in how patients feel. Evidence from PROMS is also import for downstream HTA evaluation.	
Lines 351-357 External controls		Comment: The reflection paper states that efficacy assessment can be via direct comparison against external clinical data "in	

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		exceptional circumstances." Yet we note that EMA approvals of gene therapy products up the end of 2021 have, in several cases, included comparison against an external control.[4] **We believe that any SAT serving a pivotal trial in a regulatory package must include an appropriate external control arm**. This is especially important if the marketing authorisation application relies on a single pivotal SAT. **We believe that a reflection paper for SATs is therefore incomplete without clear guidance on how to establish external control arms.** We would like to see clear guidance on: - historical control arms using real world data from registries (such as the EMA-approved ECFSPR) - contemporaneous control data from concurrent clinical trials, and how to handle potential biases - historical control data from the control arms of clinical trials conducted by multiple commercial sponsors, and how issues around data protection and commercial sensitivities may be resolved. We believe that all stakeholders, especially patients, would benefit from breaking down data silos and re-utilising data.	

[4] Iglesias-Lopez et al, 2021 doi: 10.3389/fphar.2021.773712

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40-43 Safety		Comment: This reflection paper is focused on the challenges of establishing efficacy from SATs. While the introduction states that many of the challenges and considerations equally apply to the assessment of safety, we believe that efficacy must always be considered in tandem with safety. We suggest that further guidance on SATs should consider both efficacy and safety.	