Technical Position Statement on the Use of Trikafta® in People with Cystic Fibrosis Carrying Rare Genetic Variants in Brazil

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1. Introduction

Cystic fibrosis (CF) is a genetic disease caused by alterations in the CFTR gene (cystic fibrosis transmembrane conductance regulator), which lead to dysfunction of the protein of the same name (CFTR), a "chloride channel," resulting in abnormalities of secretions in multiple organs of the human body. These alterations are most prominently expressed as respiratory disease (bronchiectasis and progressive lung disease) and gastrointestinal disease (pancreatic insufficiency and food malabsorption) (1).

More than 2,000 genetic variants of the CFTR gene have been identified. The F508del variant is the most frequent worldwide, being present in 60–70% of people with CF in Brazil, although it is less frequent compared with North American and European countries due to population origin and migratory patterns (3).

CFTR variants are classified into six groups according to the functional defect of the CFTR protein:

- **Class I:** Absence of protein synthesis
- **Class II:** Defective processing/maturation of the protein (e.g., F508del)
- **Class III:** Defects in channel regulation and gating
- **Class IV:** Defective channel conductance
- **Class V:** Reduced quantity of protein
- **Class VI:** Protein instability at the cell membrane

Classes I, II, and III are considered more severe, as they significantly impair chloride ion transport. Classes IV, V, and VI usually result in some residual protein function, generally leading to milder phenotypes. Understanding this classification is fundamental for guiding personalized therapies, such as CFTR modulators, which aim to correct or enhance protein defects (1).

Historically, the treatment of people with CF was based solely on preventing and managing disease consequences (avoiding secretion accumulation and respiratory infections, using nutritional supplements, and replacing pancreatic enzymes). Over the past 15 years, treatment has been completely transformed with the discovery of CFTR modulators—medications that act directly on the affected protein, correcting its conformation and increasing its expression and function in cells (1,2).

One such medication, Trikafta® (a combination of elexacaftor, tezacaftor, and ivacaftor), was incorporated into the Brazilian Unified Health System (SUS) in 2024 and made available to people with CF aged six years or older with at least one copy of the F508del variant.

There is a growing body of scientific evidence regarding the effects of Trikafta® in individuals without the F508del variant, carrying less frequent genetic variants known as "non-F" variants. Notably, the Trikafta® product label in Brazil was recently updated (4) to include more

than one hundred additional non-F variants responsive to treatment, based on clinical data or cell-based experiments (Table 1), thereby expanding access to this therapy.

Because the number of individuals with non-F variants is small, there is great difficulty in organizing traditional randomized controlled clinical trials for this group. Consequently, the strategy adopted in several countries has been the use of clinical trials with close monitoring of efficacy outcomes to determine whether treatment should be continued.

Using this approach, patients in France were given the opportunity to receive Trikafta® (Kaftrio®) to assess clinical and functional response in two real-world studies conducted by CF specialists in agreement with the French Ministry of Health (5,6). Individuals with CF carrying non-F variants received the medication for 4 to 6 weeks and had their outcomes evaluated by a committee of three specialists, considering clinical response, pulmonary function tests, and sweat chloride concentration (5,6). Treatment was continued only in individuals with clinical and functional response and discontinued in non-responders. Data from these studies identified several genetic variants responsive to Trikafta®, including many not listed in the U.S. product label (5,6).

This appears to be the only feasible pathway for individuals with rare non-F CFTR variants who will never be included in traditional clinical trials due to their very small numbers. The results of these studies influenced the recent decision of the European regulatory agency to expand access to the medication for people with CF with potentially responsive variants, as detailed below.

2. Regulatory Status in Brazil and Eligible Patients

In Brazil, Trikafta® received approval from ANVISA for use in people with CF from two years of age, carrying at least one copy of the F508del variant, or aged six years or older with other rare CFTR variants listed in Table 1 (4). In 2026, an expansion of access to the medication within the SUS will be requested to cover all eligible individuals in the country, in accordance with the ANVISA-approved label.

3. Regulatory Status in Other Countries

Trikafta® is approved by the U.S. Food and Drug Administration (FDA) for use in people with CF aged two years or older who carry any of 272 different CFTR variants, based on results from clinical studies and modified cell assays (7).

Taking into account the expanded U.S. label and data from the French real-world studies, the European Medicines Agency (EMA) decided in February 2025 to broaden access to the medication for all individuals with CF aged two years or older who have at least one CFTR variant other than class I variants (i.e., potentially responsive to the medication) (8,9).

Following EMA recommendations, access expansion was also granted in the United Kingdom in July 2025, when the National Health System (NHS) approved use of the medication for all individuals with CF over two years of age with any variant other than class I (10).

Table 1. Variants included in the Trikafta® label as eligibility criteria for use of the medication.

Tabela 8: Lista de mutações no gene *CFTR* que são responsivas a TRIKAFTA®				
3141del9	*E193K*	*H939R*	*N1088D*	*R1070W*
546insCTA	*E292K*	*H939R;H949L*	*N1303I*	*R1162L*
5T;TG12	*E403D*	*H1054D*	*N1303K*	*R1283M*
5T;TG13	*E474K*	*H1085P*	*P5L*	*R1283S*
296+28A→G	*E588V*	*H1085R*	*P67L*	*S13F*
621+3A→G	*E822K*	*H1375P*	*P140S*	*S108F*
711+3A→G	*E831X*	*I105N*	*P205S*	*S341P*
1341G→A	*F191V*	*I125T*	*P499A*	*S364P*
1507_1515del9	*F200I*	*I148N*	*P574H*	*S492F*
1898+3A→G	*F311del*	*I148T*	*P750L*	*S549I*
2183A→G	*F311L*	*I175V*	*Q98R*	*S549N*
2752-26A→G	*F508C*	*I331N*	*Q237E*	*S549R*
2789+5G→A	*F508C;S1251N**	*I336K*	*Q237H*	*S589N*
2789+2insA	*F508del*	*I502T*	*Q359R*	*S737F*
3041-15T→G	*F575Y*	*I506L*	*Q493R*	*S912L*
3272-26A→G	*F587I*	*I556V*	*Q552P*	*S945L*
3600G→A	*F1016S*	*I601F*	*Q1291R*	*S977F*
3849+4A→G	*F1052V*	*I618T*	*Q1313K*	*S1045Y*
3849+40A→G	*F1074L*	*I807M*	*Q372H*	*S1118F*
3849+10kbC→T	*F1099L*	*I980K*	*R31C*	*S1159F*
3850-3T→G	*F1107L*	*I1027T*	*R31L*	*S1159P*
4005+2T→C	*G27E*	*I1139V*	*R74Q*	*S1251N*
A46D	*G27R*	*I1269N*	*R74W*	*S1235R*
A62P	*G85E*	*I1366N*	*R74W;D1270N**	*S1255P*
A107G	*G126D*	*K162E*	*R74W;V201M**	*T338I*
A120T	*G178E*	*K464E*	*R74W;V201M;D1270N**	*T351I*
A234D	*G178R*	*K1060T*	*R75L*	*T1036N*
A309D	*G194R*	*L15P*	*R75Q*	*T1053I*
A349V	*G194V*	*L137P*	*R117C*	*T1086I*
A455E	*G314E*	*L165S*	*R117C;G576A;R668C*	*T1246I*
A554E	*G424S*	*L206W*	*R117G*	*T1299I*
A1006E	*G463V*	*L320V*	*R117H*	*V201M*
A1067P	*G480C*	*L333F*	*R117L*	*V232D*
A1067T	*G480S*	*L333H*	*R117P*	*V392G*
C491R	*G551A*	*L346P*	*R170H*	*V456A*
D110E	*G551D*	*L441P*	*R258G*	*V456F*
D110H	*G551S*	*L453S*	*R297Q*	*V603F*
D192G	*G576A*	*L619S*	*R334L*	*V562I*
D443Y	*G970S*	*L967S*	*R334Q*	*V754M*
*D443Y;G576A;R668C**	*G576A;R668C**	*L997F*	*R347H*	*V1153E*
D565G	*G622D*	*L1011S*	*R347L*	*V1240G*
D579G	*G628R*	*L1077P*	*R347P*	*V1293G*
D614G	*G970D*	*L1324P*	*R352Q*	*W361R*
D836Y	*G1047R*	*L1335P*	*R352W*	*W1098C*
D924N	*G1061R*	*L1480P*	*R516S*	*W1282R*
D979V	*G1069R*	*M150K*	*R553Q*	*Y109N*
D993Y	*G1123R*	*M152V*	*R555G*	*Y161D*
D1445N	*G1244E*	*M265R*	*R668C*	*Y161S*
D1152H	*G1247R*	*M952I*	*R709Q*	*Y301C*
D1270N	*G1249R*	*M952T*	*R751L*	*Y563N*
E56K	*G1349D*	*M1101K*	*R792G*	*Y1014C*
E60K	*H139R*	*M1137V*	*R933G*	*Y1032C*
E92K	*H199Y*	*N186K*	*R1048G*	
E116K	*H620P*	*N187K*	*R1066H*	
E116Q	*H620Q*	*N418S*	*R1070Q*	

* Mutações complexas/compostas, em que um único alelo do gene *CFTR* tem várias mutações; elas existem independentemente da presença de mutações no outro alelo.

4. Pathophysiological Rationale and Mechanism of Action

The elexacaftor/tezacaftor/ivacaftor combination (Trikafta®) acts as a CFTR protein modulator through the following mechanisms:

1. **Correctors** (elexacaftor and tezacaftor) address the basic protein defect, increasing processing, trafficking, and expression of functional CFTR protein at the cell surface.
2. **Potentiator** (ivacaftor) improves the probability of chloride channel opening, enhancing chloride flow (activating channel function).

These mechanisms make it plausible that CFTR proteins with defects in processing, trafficking, or gating may respond to therapy, which supports the concept of "theratyping" (classification of variants based on their response to modulators in vitro or ex vivo) (11,12).

5. Evidence for Individuals with Rare Variants Not Included in the Current Trikafta® Label

The **R334W variant** (c.1000C>T or p.Arg334Trp) is a class IV variant with variable clinical impact, including reports of later diagnosis, lower frequency of pancreatic insufficiency, and differences in respiratory infection patterns compared with F508del. In Brazil, this is the fourth most frequent variant, present in 296 alleles. Recent studies have demonstrated rescue of CFTR function with CFTR modulators (13), and the French real-world study included 14 individuals with the R334W variant (without F508del) (5). Mean sweat chloride concentration decreased from 103 (91–105) mmol/L to 85 (66–91) mmol/L, and pulmonary function improved with mean FEV_1 increasing from 67% (42–102%) to 83% (56–101%) after Trikafta® (Kaftrio®). A mean weight gain of approximately 4 kg was also reported, along with improvements in quality of life, symptoms, and respiratory exacerbations. This variant was classified as responsive to the medication (5).

The **R1066C variant** (c.3196C>T or p.R1066C) is a class II variant with severe clinical consequences similar to those observed with F508del. In Brazil, it is the eighth most frequent allele, present in 161 alleles. Ex vivo studies report rescue of CFTR function with Trikafta®, reaching approximately 50% of normal function after exposure (14), noting that at least 10% activity is estimated to be required for clinical impact. In the French real-world study, 8 individuals with this variant (without F508del) were included, showing clear clinical and functional benefit, with mean sweat chloride decreasing from 102 (96–107) mmol/L to 60 (48–80) mmol/L and mean FEV_1 increasing from 63% (27–90%) to 75% (42–124%) after treatment (5).

6. Non-F Variants in Brazil

The frequency of CFTR gene variants in people with CF in Brazil is described in reports from the Brazilian Cystic Fibrosis Registry (REBRAFC). More than 300 variants have been identified in Brazilian individuals with CF, most occurring in a small number of patients. Data from

the 2023 report (www.gbefc.org.br) present the 15 most frequent variants and their eligibility for CFTR modulator therapy, as shown in Table 2.

Table 2. Most frequent CFTR gene variants among people with CF in Brazil and their eligibility for Trikafta® use.

Ranking	Variante	Número de alelos	% do total de alelos
1	F508del	5226	50,66
2	G542X	782	7,58
3	3120+1G->A	347	3,36
4	R334W	296	2,87
5	R1162X	248	2,4
6	G85E	200	1,94
7	S549R	165	1,6
8	R1066C	161	1,56
9	N1303K	137	1,33
10	S4X	134	1,3
11	3272-26A->G	125	1,21
12	Y1092X	112	1,09
13	5T	97	0,94
14	2184delA	92	0,89
15	P205S	86	0,83

Note: each individual has two CFTR alleles; therefore, it is not possible to determine the exact number of individuals with each variant based on this table.

Legend:

- Eligible for Trikafta® in the SUS
- Not eligible for CFTR modulators
- Eligible for Trikafta® according to real-world studies
- Eligible for Trikafta® according to the ANVISA-approved label (March 2025)
- Eligible for Ivacaftor in the SUS

A document presenting estimates of individuals potentially eligible for Trikafta® treatment with non-F variants was published last year on the GBEFC website, the organization responsible for managing the REBRAFC (15). That document did not include the two main variants in Brazilian

individuals not listed on the Trikafta® label (R334W and R1066C), whose frequencies are shown in Table 3.

Table 3. Number of non-F individuals with CFTR variants R334W and R1066C. Total cases: 199 individuals (two individuals carry both variants).

	< 2 years	2 to < 6 years	6–12 years	≥ 12 years
R334W heterozygous	2	5	18	92
R334W homozygous	0	0	0	11
R1066C heterozygous	3	8	14	38
R1066C homozygous	0	2	6	2
Total	5	15	38	143

7. Position of GBEFC Professionals on the Issue

The purpose of this publication is to provide evidence-based support for judicial decisions and for Technical Notes issued by the Judiciary Technical Assistance Center (NATJUS), in light of the complexity of the topic involving coverage of modulator therapy (such as Trikafta®) for patients with mutations that are not explicitly listed in the drug label. In this context, we have identified divergences in some Technical Notes regarding the interpretation of the circumstances under which a "rare mutation" is or is not covered, based exclusively on in vitro evidence or real-world studies. We therefore aim to add knowledge and contribute to decision-making supported by scientific evidence.

Trikafta® already has a robust international regulatory basis for the treatment of cystic fibrosis in individuals carrying the F508del variant and, increasingly, for hundreds of non-F508del variants with evidence of response to therapy (in vitro or clinical). In Brazil, the recent ANVISA label update includes younger individuals (from two years of age) and rare variants with evidence of functional response. However, it still does not include ultra-rare variants with evidence of response from functional or clinical studies (16), which we consider a critical issue when dealing with ultra-rare conditions, favoring broader access approaches such as those adopted by the European agency and the United Kingdom.

GBEFC specialists align with the perspective of the European agency and the United Kingdom: for a severe, progressive, and debilitating disease such as CF, expanding access with careful monitoring of treatment response has scientific and clinical justification, is essential, and should be viewed as an undeniable right to health for Brazilian individuals with CF. Therefore, **we believe that every Brazilian diagnosed with cystic fibrosis aged two years or older, with at least one CFTR variant potentially responsive to Trikafta®, should have immediate access to the**

medication, **conditional upon evaluation of treatment response by specialists.** This conditional approach implies that non-responsive individuals should discontinue use of the medication.

This broader access strategy places significant responsibility on involved specialists to assess clinical and functional response using clearly defined and objective outcomes. New evidence on variants with potential responsiveness to Trikafta® (as well as identification of non-responsive variants) continues to emerge (17,18), reinforcing the importance of evidence-based, individualized assessments.

The current CF care landscape in Brazil is well organized, with most patients monitored in Specialized CF Reference Centers. GBEFC has played a pioneering role in the continuous generation of knowledge on CF diagnosis and treatment in Brazil through the REBRAFC and stands ready to support the Ministry of Health in managing access for rare off-label cases by providing objective outcome data, reducing burden, and offering technical support to decisions within the Brazilian judicial system.

ABOUT THE BRAZILIAN CYSTIC FIBROSIS STUDY GROUP (GBEFC):

The GBEFC is a non-profit organization composed of healthcare professionals working in the field, founded on November 5, 2003. Among its activities, the GBEFC is responsible for the creation and maintenance of the Brazilian Cystic Fibrosis Registry, conducting research, training healthcare professionals, and supporting the implementation of Cystic Fibrosis treatment centers across the country. In addition, it organizes national congresses on the disease and collaborates with the Ministry of Health in the development of national care protocols for Cystic Fibrosis.

8. Bibliography

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