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Worries Over EU JCAs Push Telethon To Speed Up Gene Therapy Filing Plan

by Francesca Bruce

High patient expectations also drove Telethon's decision to bring forward its marketing authorization application plans for its ultra rare disease gene therapy, etuvetidigene autotemcel.

The risks posed by forthcoming EU-level joint clinical assessments (JCAs) is "one of the key factors" driving Fondazione Telethon's decision to file its marketing authorization application (MAA) for its investigational gene therapy etuvetidigene autotemcel "as early as possible."

Fondazione Telethon plans to file its MAA with the European Medicines agency before the JCAs go live for advanced therapies and oncology products from 12 January 2025, Stefano Benvenuti, public affairs manager at the not-for-profit organization, told the *Pink Sheet*.

Etuvetidigene autotemcel targets Wiscott-Aldrich Syndrome (WAS), a rare X-linked condition characterized by thrombocytopenia.

The threat to cross-border access to ultra rare disease treatments such as Telethon's gene therapy outweigh the potential benefits of a JCA, Benvenuti said.

JCAs will be similar to relative effectiveness assessments currently carried out by EU member state authorities and will be conducted on an EU level. They must be considered by all member state health technology assessment (HTA) bodies or national pricing and reimbursement authorities in their decision making.

Key Takeaways

- Fondazione Telethon has decided to file for EU marketing authorization before joint clinical assessments come into force.

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The assessments are being introduced under the 2022 Health Technology Assessment Regulation, aims to improve cooperation on HTA across the bloc, cut duplication of effort and speed up decision making. A JCA for a drug is to start when the European Medicines Authority confirms it has received a marketing authorization application for the product.

Telethon wants to make sure its MAA is filed before the requirement for a JCA kicks in.

- Evidence from a single-arm study mean there is too great a risk of a negative JCA outcome, which could encourage member state authorities to decline requests for cross border treatment in other countries.
- An advanced development program and high patient expectations were also behind the decision to file early.

Concern about JCAs has been mounting, for example companies are worried about timelines, the scoping policies involved and access to scientific advice. (Also see "*Lack Of Industry Involvement In EU HTA Scoping Process Exacerbates 'Unworkable' Timelines*" - Pink Sheet, 19 Apr, 2024.) There is also significant apprehension surrounding JCA evidence requirements, which prompted non-profit organizations to issue a call to action to prevent these requirements from becoming a barrier to access to medicines. (Also see "*Non-Profit Groups Rally To Remedy EU Joint Clinical Assessment Evidence Issues*" - Pink Sheet, 17 Jul, 2024.) Telethon, along with the Alliance for Regenerative Medicine and the patient group Cancer Patients Europe, led the call for action.

The anxieties about evidence relate to two sets of guidelines, published in March primarily for assessors, on indirect and direct comparisons for generating evidence for the JCAs: "Practical Guidelines for Quantitative Evidence Synthesis: Direct and Indirect Comparisons" and "Methodological Guidelines for Quantitative Evidence Synthesis: Direct and Indirect Comparisons."

Particularly worrisome was a statement in the methodological guideline on the use of non-randomized studies that says: "For some interventions, single-arm or non-randomised evidence may be the only evidence available for consideration. However, it may well be that this evidence is insufficient for estimation of the relative treatment effectiveness in the context of JCA."

Telethon's primary worry is that the JCAs could impact cross-border access to advanced therapies for ultra rare diseases that will only be available in a few centers in Europe, explained Benvenuti.

Under EU rules, including the Social Security Coordination Regulation, patients who want to receive treatment in another member state must receive prior authorization from their own

member state authorities.

However, "if, as stated in the current guidelines, the JCA will likely consider a single-arm trial as 'insufficient' evidence, we are worried that this could become a strong argument for health care authorities in the patient's home country not to authorize cross-border movement of patients," said Benvenuti.

Etuvetidigene autotemcel falls into this category of products and will be administered in only a few specialized treatment centers. "Being a complex procedure for an ultra-rare disease – we expect no more than five patient per year in the whole of Europe – it is extremely difficult to build the necessary expertise and experience if we spread the treatment among too many centers," he commented. Nor do patients wish to be treated in a center that administers the therapy only once every three or four years and therefore may not have the necessary experience, he added.

Moreover, the data supporting the WAS gene therapy are based on single-arm studies and there is a "strong possibility" that the evidence would not satisfy assessors.

However, filing early to avoid a JCA will also mean that the product cannot benefit from the potential advantages of a JCA. "We have always been, and still are, in favour of more centralized procedures that can facilitate a more equitable and quicker access for all EU patients. And I think JCA goes in that direction," commented Benvenuti.

Despite the potential benefits, it would be very difficult for a small organization like Telethon to prepare a "robust JCA dossier within the given timeframe and with the data we have at the moment (ie, clinical evidence only from single-arm trial and expanded access programs)," said Benvenuti. "The guidelines have just been published and we cannot afford additional studies to build a more robust HTA," he said.

Patient Expectation

As important a consideration as it was, the JCA was not the only factor influencing Telethon's filing decision. The development program for etuvetidigene autotemcel was very advanced when Telethon reacquired the rights to the product (formerly called OTL-103) from Orchard Therapeutics in February. The gene therapy was initially developed by the San Raffaele-Telethon Institute in Milan and was part of a partnership with Orchard.

Given that Orchard had announced plans to file for marketing authorization in mid-2022, before announcing it would disinvest from the immunodeficiency space, patient community expectations were very high, said Benvenuti.

Telethon therefore took steps to initiate an early access program approved by Italy's regulator,

AIFA. It also decided to take part in the EMA's pilot program designed to support academic and non-profit developers of advanced therapy medicinal products that address unmet medical need. In February 2024, the EMA announced that it had selected Telethon and etuvetidigene autotemcel for the pilot.

The organization also decided to "speed-up the process for MAA [marketing authorization application] submission."

Benvenuti commented that he was not aware of other developers accelerating their plans to file their MAAs to avoid a JCA. "Most for-profit developers accelerate the MAA anyway, whenever possible, as that is their core business," he said.

Telethon conducts research into and markets advanced therapies. It also acquired the EU marketing authorization for Orchard's Strimvelis in September 2023. Strimvelis is a gene therapy is used to treat adenosine deaminase severe combined immunodeficiency (ADA-SCID).