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Alvotech's Latest FDA Knockback Cuts It Fine For Humira Rival

AVT02 Adalimumab Biosimilar Receives A Further CRL From US Regulator After Inspection

by David Wallace

Alvotech has received a further complete response letter from the US FDA relating to its AVT02 proposed adalimumab biosimilar rival to Humira. The latest BsUFA goal date disclosed for the product is now just a few days ahead of a potential US launch.

Alvotech has received another setback on its attempts to gain US approval for its AVT02 biosimilar rival to Humira (adalimumab), after the US Food and Drug Administration issued a complete response letter over deficiencies at the firm's Reykjavik manufacturing facility.

This followed an earlier CRL issued by the FDA over the high-concentration 100mg/ml version of adalimumab. (Also see "*Alvotech Bullish As Facility Deficiencies Hold Up Humira Biosimilar Again*" - Generics Bulletin, 6 Sep, 2022.)

Alvotech had previously disclosed an FDA action date of 13 April for AVT02, provided that it resolved issues in the earlier CRL, with the company lining up an early March inspection for the Reykjavik plant. (Also see "*Alvotech Lines Up FDA Inspection Ahead Of Adalimumab Action*" - Generics Bulletin, 19 Jan, 2023.) (Also see "*Alvotech Awaits Date With Destiny, With FDA Inspection To Begin On 6 March*" - Generics Bulletin, 3 Mar, 2023.)

But now, the company has announced that the latest CRL "noted that certain deficiencies, which were conveyed following the FDA's reinspection of the company's Reykjavik facility that concluded on 17 March 2023, must be satisfactorily resolved before the application can be approved."

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"No other deficiencies in the application were noted by the FDA," Alvotech underlined. The firm added that it had "provided the FDA comprehensive responses to the inspection observations on 3 April 2023, and is awaiting communication from the agency assessing those responses."

However, a potential approval for AVT02 could still be in sight within a couple of months, Alvotech suggested, as the firm had a parallel biosimilar filing on record with the FDA – this one containing additional information to support approval of AVT02 as an interchangeable biosimilar – with the FDA having provided a goal date for this application of 28 June 2023.

This would be just three days before the 1 July US launch date that Alvotech secured for AVT02 through a settlement with originator AbbVie last year. (Also see "*Alvotech Humira Settlement Sets Up Interchangeable Adalimumab Showdown*" - Generics Bulletin, 9 Mar, 2022.)

Nevertheless, "satisfactory outcome of the facility reinspection remains the key requirement for approval," Alvotech highlighted.

The FDA has already indicated that it has "completed review of Alvotech's application of AVT02 as interchangeable to high-concentration Humira and confirmed that the data provided are sufficient to support a determination of interchangeability" (*see sidebar*). However, this approval can only happen if the agency is satisfied with Alvotech's facility.

FDA Promises Interchangeability For Alvotech's 100mg/ml Humira Rival – If It Passes Inspection

By David Wallace

22 Dec 2022

Alvotech has been bolstered by a US FDA confirmation that its AVT02 adalimumab candidate can be approved as an interchangeable biosimilar based on the data provided in its filing – but first, the Icelandic firm must pass an upcoming facility inspection.

Read the full article here

Robert Wessman, founder chairman and CEO of Alvotech, said the firm would "look forward to working with the FDA to resolve any outstanding issues identified in the reinspection."

"We are committed to manufacturing AVT02 for patients in the US," he insisted, "especially a potentially differentiated Humira biosimilar that provides a high-concentration formulation and is interchangeable."

Teva Optimistic Despite 'Disappointing' Outcome

Meanwhile, US marketing partner *Teva* also commented on the CRL, acknowledging that "the application could not be approved at this time based on deficiencies associated with Alvotech's manufacturing facility that must be satisfactorily resolved" and confirming that

“additional review of the details following the recent FDA’s re-inspection and CRL are being assessed to determine next steps.”

“While this outcome is disappointing, Teva remains fully committed to its leadership in biosimilars and the partnership with Alvotech,” the firm stated. “The company remains optimistic about additional compounds in the pipeline and further progress with AVT02.”

Biosimilars covered by the Teva-Alvotech alliance (Also see "*Teva And Alvotech Strike US Biosimilars Pact*" - Generics Bulletin, 5 Aug, 2020.) include Alvotech’s AVT04 proposed ustekinumab biosimilar. (Also see "*Alvotech And Teva File US Stelara Rival Ahead Of 2023 Expiry*" - Generics Bulletin, 6 Jan, 2023.)

The US FDA is something of an outlier on AVT02, with the adalimumab biosimilar having already been approved by the European Medicines Agency, allowing European marketing partner Stada to launch the product as Hukyndra last year. (Also see "*Stada And Alvotech Launch Higher-Strength Adalimumab In Europe*" - Generics Bulletin, 9 Jun, 2022.)

Approvals have also been received in Canada – where AVT02 was launched by local partner Jamp under the Simlandi brand name (Also see "*Canada Sees Face-Off Over Higher-Strength Adalimumab*" - Generics Bulletin, 14 Apr, 2022.) – as well as in territories such as Australia and Saudia Arabia. (Also see "*Alvotech Taps Equity Financing As Venture Bears Fruit In Saudi Arabia*" - Generics Bulletin, 25 Jan, 2023.)

AVT02 Has Potential To Take Leading Role Among US Biosimilars

The latest FDA CRL imperils the potential for Alvotech and Teva to take a leading position among Humira challengers when a second wave of biosimilar competition hits the US later this year (*see sidebar*), following Amgen’s launch of first biosimilar Amjevita (adalimumab-atto) at the end of January. (Also see "*Amgen Delivers On Launch Of First US Humira Rival – At A 55% Discount*" - Generics Bulletin, 31 Jan, 2023.)

In an 11 April note, Evercore suggested that Amgen had seen a fairly slow start in terms of uptake for its adalimumab biosimilar, but that Teva and Alvotech could be better positioned in the market, thanks to attributes of AVT02 that distinguished it from other Humira rivals, including Amjevita.

“Amgen recently launched the first biosimilar – and only did $0.5m in IMS

Humira In 2023: The $17bn Biosimilar Opportunity

By David Wallace

05 Jan 2023

The advent of US biosimilar competition to Humira in 2023 represents the largest ever

sales in [the] first month of launch," Evercore noted. "That's underwhelming. There's clearly a misaligned incentives issue with managed care and rebates." (Also see "*Amgen Talks Dual Pricing Strategy For Amjevita*" - Generics Bulletin, 1 Feb, 2023.)

But there was "also an imperfect product profile with [the] Amgen launch," Evercore said, with Amjevita being a lower-strength 50mg/ml biosimilar rather than a 100mg/ml high-concentration version, and with the Amgen product also not boasting an interchangeability designation.

loss-of-exclusivity opportunity for the off-patent industry, with the first adalimumab rival expected to hit the US market at the end of this month. But with a host of other biosimilars expected to launch throughout the year, how will competition play out in the long term?

Read the full article here

The analyst suggested that "Teva's biosimilar is very important for three reasons: it is high concentration (which is how AbbVie markets Humira now; to my knowledge, only a few biosimilars will have a high concentration version in 2023); it could be interchangeable (data has been submitted for that); and it is likely one of the "two to three" biosimilars that managed care may actually put on formulary." (Also see "*Optum Rx Reveals Humira Biosimilar Plan To 'Support Advancement Of The Market'*" - Generics Bulletin, 2 Dec, 2022.)

Follows Increase In Alvotech Share Holding

The latest news on AVT02 follows an announcement by Alvotech at the end of March that it was increasing its share capital and ownership of its own shares.

"The board of directors has resolved to increase the company's share capital by an amount of $140,057.90 by issuing 14,005,790 ordinary shares," Alvotech announced on 28 March. "The company's subsidiary, Alvotech Manco ehf., has subscribed to all of the newly issued shares for a price of $13.51 per share," with the shares held by the subsidiary "treated as treasury shares without voting rights or dividend entitlement."

"Following the above-mentioned transactions, the subsidiary will hold 26,212,633 shares in the company, or around 9% of issued shares, and the number of issued shares has increased from 275,721,672 to 289,727,462 shares."

This follows the completion on 10 February 2023 of a private share placement. (Also see "*Alvotech Taps Equity Financing As Venture Bears Fruit In Saudi Arabia*" - Generics Bulletin, 25 Jan, 2023.)

"When the transaction was settled, 11,834,061 shares previously held by the subsidiary were

transferred to the investors," Alvotech noted. "The share capital increase is intended to meet the reduction in the number of treasury shares which resulted from the above-mentioned settlement, allowing the company to continue holding a sufficient number of shares to fulfill the company's commitments related to various financial obligations, including warrants, convertible financial instruments and share-based employee compensation."