SCRIP
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Bangers In MASH: How Rezdiffra's Rivals Stack Up

by Elizabeth Cairns

A look at the depth of clinical responses seen with various MASH therapies suggests that Madrigal could eventually face serious competition.

Madrigal Pharmaceuticals, Inc.'s Rezdiffra (resmetirom) has become the first ever approved therapy for metabolic-associated steatohepatitis (MASH). The company has a lead of a couple of years over its next most advanced competitor, *Novo Nordisk A/S*'s semaglutide, in the disorder – but how does Rezdiffra stack up clinically?

The analyses below use reported data from the Phase II trials of selected MASH agents and pit them against Rezdiffra's showing in its Phase III study. They show the improvements they have achieved on various endpoints – and, crucially, how these change over time. And interestingly, several of the newer products appear to outplay Madrigal's first-mover.

Key Takeaways

- Madrigal's Rezdiffra has just been approved for MASH
- But upcoming drugs could be more effective

The graphs below compare data from different studies, with different enrolment criteria and designs. They must, therefore, be treated with caution since only a head-to-head trial can provide a truly robust comparison.

The two crucial endpoints for MASH products to hit are improvement in fibrosis (defined as reduction by at least one stage, on a scale from 0 to 4, with higher stages indicating greater

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severity), with no worsening of MASH, and MASH resolution without worsening of fibrosis (defined as an increase of at least one stage).

It should be noted that when most of these trials reported, the companies and researchers used the old term for MASH, nonalcoholic steatohepatitis. (Also see "*Say Goodbye To NASH And Hello To MASH*" - Scrip, 6 Mar, 2024.)

On the first of these important goals, fibrosis improvement, Rezdiffra appears to beat Novo's semaglutide. But no fewer than three of the Phase II-stage contenders – *Akero Therapeutics, Inc.*'s efruxifermin and *89bio, Inc.*'s pegozafermin, both FGF21 analogs, as well as *Inventiva S.A.*'s PPAR agonist lanifibranor – look better, at least at their higher doses.

Madrigal's FDA Approval In MASH Ends Years Of Industry Frustration

By Joseph Haas and Mary Jo Laffler

14 Mar 2024

As the first approved MASH (formerly NASH) therapy, nearly four years after initially anticipated, Madrigal gets the opportunity to establish a MASH marketplace with Rezdiffra (resmetirom).

Read the full article here

That said, recent 96-week data on Akero's therapy, while notable, appear to show a slowing of the rate of improvement from the 24 week data cut – the time point for the HARMONY trial's primary endpoint. (Also see "*Akero's 96-Week Fibrosis Data Sparkle In MASH*" - Scrip, 5 Mar, 2024.)

A late entrant is *Ionis Pharmaceuticals, Inc.*'s antisense product ION224, which on 13 March was revealed to have shown a respectable improvement on this goal at 51 weeks. (Also see "*Ionis Could Be A Factor In MASH With Positive Phase II Data*" - Scrip, 13 Mar, 2024.)

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When the rivals' performance on the MASH resolution endpoint is plotted against time, a similar pattern may be discerned – only here, efruxifermin's efficacy really did wane over time, at least for the highest dose. At 24 weeks, the delta over placebo on MASH resolution with efruxifermin 50mg was 61 points in the HARMONY trial. This had shrunk to just 33 points by week 96.

One drug worth keeping an eye on here is *Eli Lilly and Company*'s tirzepatide. The GIP/GLP agonist achieved an impressive level of MASH resolution after a year's treatment in its Phase II SYNERGY-NASH study. (So far, Lilly has not released data on fibrosis improvement from SYNERGY-NASH.)

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Of note, this analysis suggests that Rezdiffra is in fact the weakest of these MASH drugs as far as MASH resolution is confirmed. Perhaps there is room for improvement

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Biomarkers

Some MASH candidates, however, have not yet reached the stage of demonstrating improvements on these biopsy-based measures. For now, their potential can only be judged on biomarker-based findings.

One of the most common of these is magnetic resonance imaging proton density fat fraction (MRI-PDFF), a noninvasive, quantitative, imaging-based biomarker of liver fat content. This analysis, too, shows Rezdiffra coming off relatively poorly. Earlier-stage candidates from *Viking Therapeutics, Inc.*, *Terns Pharmaceuticals, Inc.* and *Boston Pharmaceuticals Inc.* show steeper liver fat cuts, albeit with shorter treatment durations.

Rezdiffra is the first drug available to treat MASH – but, ultimately, it might not be the best.

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