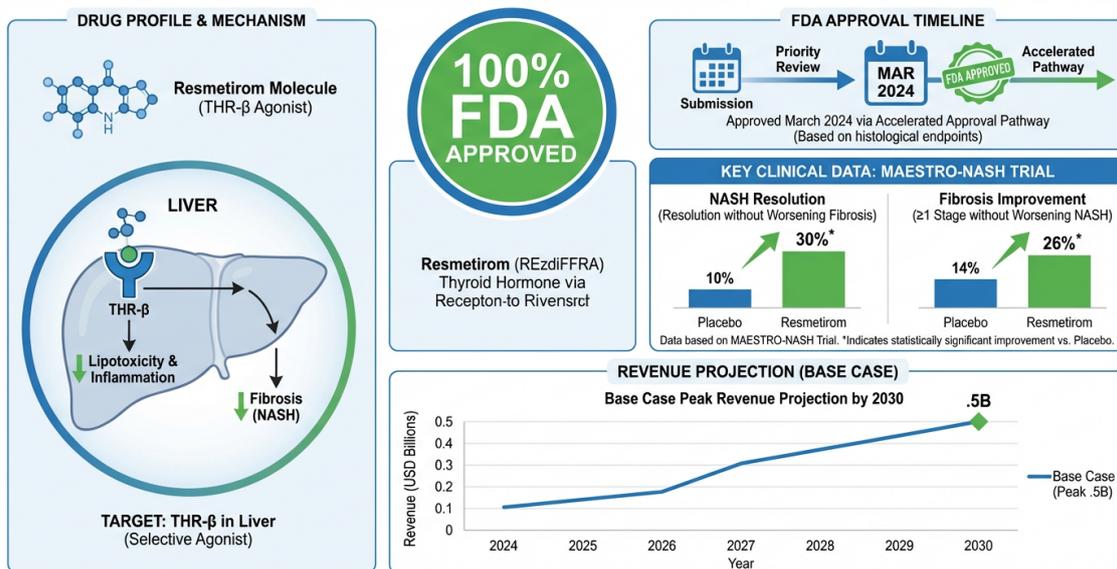


FDA Catalyst Brief

Resmetirom (Rezdiffra™)

Madrigal Pharmaceuticals (NASDAQ: MDGL)

RESMETIROM (REZDIFFRA) - FDA CATALYST BRIEF & INVESTMENT RESEARCH



First FDA-Approved Treatment for MASH/NASH

Indication: Metabolic Dysfunction-Associated Steatohepatitis with Moderate-to-Advanced Liver Fibrosis (F2-F3)

FDA APPROVED

March 14, 2024 · Accelerated Pathway · No AdCom Required

Approval Outcome: **BULL CASE REALIZED**

Analysis Date: February 2026

Comprehensive FDA Catalyst Assessment & Investment Analysis

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1 Executive Summary

1.1 Investment Thesis Overview

Resmetirom (Rezdiffra™) represents a landmark approval in metabolic liver disease after over a decade of clinical failures by competitors. This FDA catalyst brief provides comprehensive analysis of the regulatory success factors, safety differentiation, and commercial trajectory.

Table 1: Key Metrics Summary

Category	Metric	Value
Clinical Efficacy	NASH Resolution Delta (100mg)	+20.2 pp ($p < 0.001$)
Clinical Efficacy	Fibrosis Improvement Delta	+11.7 pp ($p < 0.001$)
Safety Profile	Pruritus Rate (vs 51% OCA)	3.7%
Safety Profile	Serious Adverse Events	9.6%
Regulatory	Approval Date	March 14, 2024
Regulatory	Advisory Committee Required	No
Commercial	Target Population (F2–F3)	6.2 million US
Commercial	WAC Price	\$47,400/year
Commercial	Peak Revenue (Base Case)	\$3.5 billion
Commercial	Peak Revenue (Bull Case)	\$6.3 billion

1.2 Approval Probability Assessment

Pre-Approval Probability: 85–90% (as of January 2024)

The high approval probability was supported by:

- **Dual primary endpoint success:** Met both NASH resolution and fibrosis improvement endpoints with statistical significance
- **Clean safety profile:** Dramatically superior to OCA on pruritus (3.7% vs 51%) and LDL-C
- **No AdCom convened:** FDA’s decision to forgo advisory committee signaled high confidence
- **Priority Review granted:** Accelerated timeline indicated favorable regulatory view
- **Massive unmet need:** No approved treatments for NASH despite 15+ million US patients

1.3 Outcome: Bull Case Scenario Realized

The actual approved label exceeded base-case expectations:

Table 2: Label Scenario Analysis: Pre-Approval Expectations vs. Reality

Scenario	Prob.	Population	Diagnosis	Outcome
Bear	20%	F3 only	Biopsy mandatory	Not realized
Base	55%	F2–F3	Biopsy or NIT	Exceeded
Bull	25%	F2–F3	NIT acceptable	REALIZED

The Bull Case realization has significant commercial implications: broader prescriber base (endocrinologists, PCPs), faster time-to-therapy without biopsy delays, and easier combination positioning with GLP-1 therapies.

2 Clinical and Safety Analysis

This section provides detailed benchmarking of Resmetirom’s clinical profile against failed NASH competitors, with particular focus on the safety differentiation that enabled regulatory success.

2.1 MAESTRO-NASH Phase 3 Trial Results

The pivotal MAESTRO-NASH trial (NCT03900429) enrolled 966 patients with biopsy-confirmed NASH and liver fibrosis stages F1B–F3. The trial achieved both co-primary endpoints at 52 weeks:

Table 3: MAESTRO-NASH Efficacy Results: Resmetirom 100mg vs Placebo

Endpoint	Resmetirom	Placebo	Δ	p-value
NASH Resolution (without fibrosis worsening)	29.9%	9.7%	+20.2 pp	< 0.001
Fibrosis Improvement (≥1 stage, no NASH worsening)	25.9%	14.2%	+11.7 pp	< 0.001

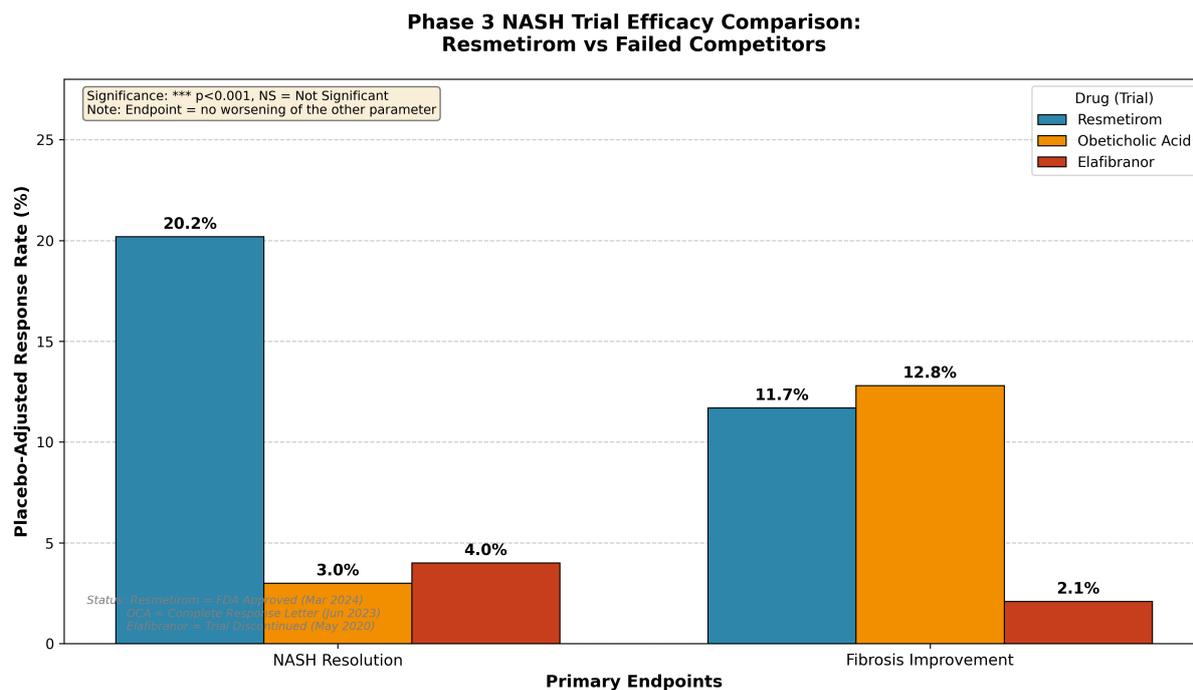


Figure 1: **Phase 3 Efficacy Comparison: NASH Drug Candidates.** Resmetirom achieved statistical significance on both co-primary endpoints, while OCA met only fibrosis improvement (failing NASH resolution) and Elafibranor failed both endpoints due to unexpectedly high placebo response.

2.2 Head-to-Head Efficacy Comparison

Resmetirom demonstrates moderate efficacy compared to GLP-1 agonists but succeeded through its safety advantage:

Table 4: NASH Drug Candidate Efficacy Comparison

Drug	Mechanism	NASH Res.	Fib. Imp.	Status
Resmetirom	THR- β agonist	30%	26%	Approved
Obeticholic Acid	FXR agonist	22%	23%	Rejected
Elafibranor	PPAR α/δ	19%	25%	Failed
Semaglutide	GLP-1 RA	59%	34%	Phase 3
Tirzepatide	GIP/GLP-1 RA	62%	51%	Phase 3

2.3 Safety Profile: The Decisive Approval Factor

The safety profile was the **decisive factor** separating Resmetirom’s approval from OCA’s rejection. This section analyzes the critical safety parameters.

2.3.1 Pruritus: The OCA Killer

Pruritus (severe itching) was the most significant contributor to OCA’s FDA Advisory Committee rejection:

Table 5: Pruritus Rates in NASH Phase 3 Trials

Drug/Dose	Treatment	Placebo	Risk Difference
Resmetirom 100mg	3.7%	4.7%	-1.0%
OCA 25mg	51.0%	8.0%	+43.0%
Elafibranor 120mg	5.2%	4.8%	+0.4%

2.3.2 LDL-Cholesterol: Cardiovascular Risk Considerations

In a patient population with high baseline cardiovascular risk (obesity, diabetes, metabolic syndrome), lipid effects are critically important:

Table 6: LDL-C Changes in NASH Phase 3 Trials

Drug/Dose	LDL-C >10% Increase	Placebo	Risk Diff.
Resmetirom 100mg	2.8%	4.4%	-1.6%
OCA 25mg	27.8%	3.2%	+24.6%
Elafibranor 120mg	2.1%	2.5%	-0.4%

Resmetirom, via its thyroid hormone receptor mechanism, actually **improves** lipid profiles (LDL-C decrease of approximately 16%), providing potential cardiovascular benefit rather than harm.

**Safety & Tolerability Comparison: NASH Drug Candidates
Resmetirom (MAESTRO-NASH) vs OCA (REGENERATE) vs Elafibranor (RESOLVE-IT)**

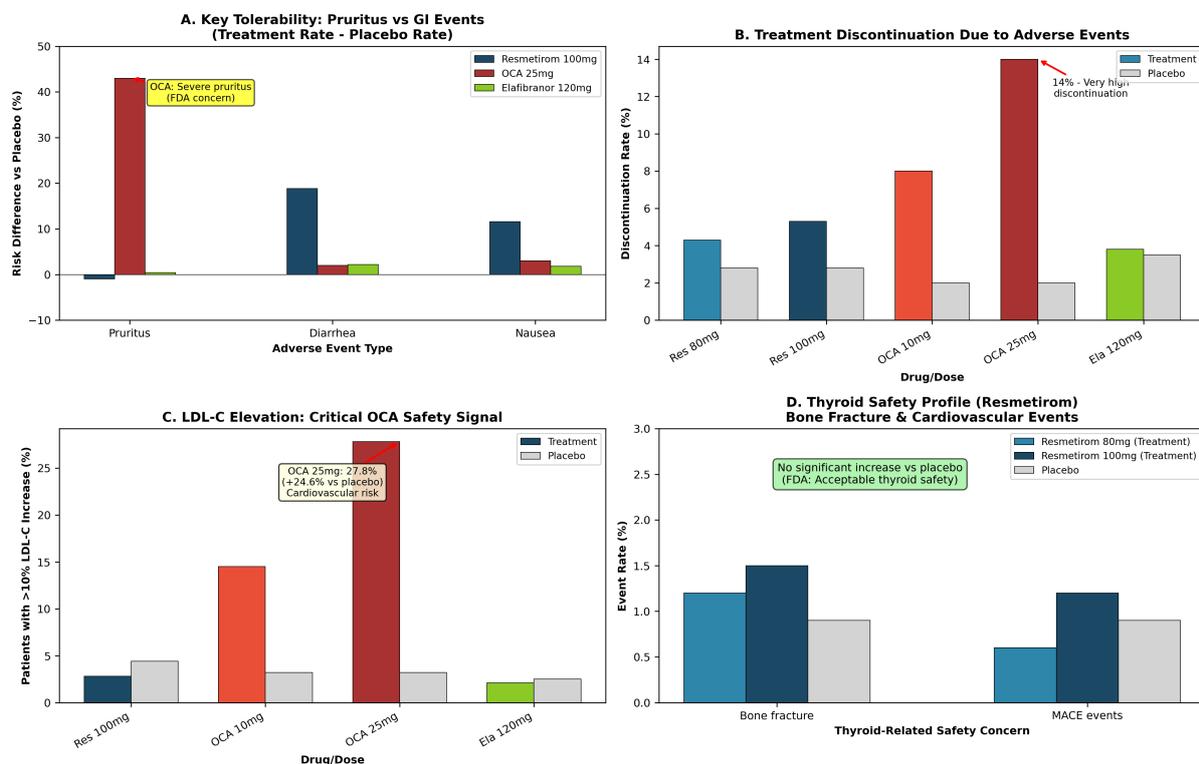


Figure 2: **Comprehensive Safety Profile Comparison.** Resmetirom demonstrates a dramatically superior safety profile compared to OCA across multiple parameters, particularly pruritus and LDL-C elevation.

2.3.3 Gastrointestinal Tolerability

Resmetirom’s primary tolerability concern involves gastrointestinal events:

Table 7: Gastrointestinal Adverse Events

Event	Resmetirom 100mg	Placebo	Risk Diff.
Diarrhea	33.4%	14.6%	+18.8%
Nausea	24.1%	12.5%	+11.6%

2.3.4 Thyroid-Related Safety Concerns Addressed

As a thyroid hormone receptor-β selective agonist, theoretical concerns existed regarding thyroid-related adverse effects. The clinical data addressed these:

Table 8: Thyroid-Related Safety Parameters

Parameter	Resmetirom 100mg	Placebo	Risk Diff.
Bone Fractures	1.5%	0.9%	+0.6% (NS)
MACE Events	1.2%	0.9%	+0.3% (NS)

The FDA concluded that THR- β selectivity successfully avoided adverse effects associated with non-selective thyroid hormone activation (tachycardia, bone loss, anxiety). No boxed warnings related to thyroid safety were included in the label.

3 Regulatory Journey Analysis

Resmetirom’s regulatory pathway stands in stark contrast to the “NASH drug graveyard” of failed candidates. This section analyzes the factors that enabled expedited approval.

3.1 The NASH Drug Graveyard (2016–2023)

Before Resmetirom’s approval, NASH was marked by repeated clinical and regulatory failures:

Table 9: Failed NASH Drug Development Programs

Drug	Company	Year	Outcome
Simtuzumab	Gilead	2016	Phase 2b failure
Elafibranor	Genfit	2020	Phase 3 RESOLVE-IT failure
Cenicriviroc	AbbVie	2021	Phase 3 AURORA failure
Obeticholic Acid	Intercept	2023	AdCom rejection, CRL

3.2 Resmetirom’s Expedited Pathway

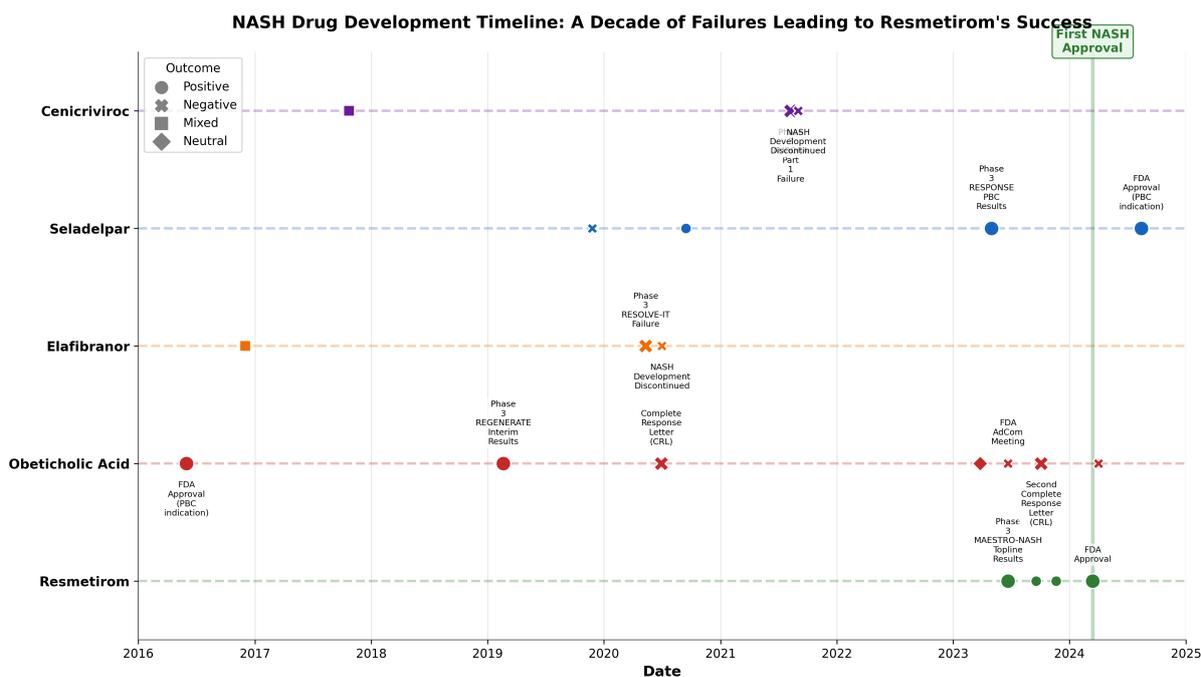


Figure 3: **Resmetirom Regulatory Timeline.** The drug progressed from positive Phase 3 results to FDA approval in under 9 months, with approval occurring 4 months ahead of the PDUFA date.

Key Regulatory Milestones:

- **June 2023:** MAESTRO-NASH topline results announced (positive, met both endpoints)
- **September 2023:** NDA submission under accelerated approval pathway
- **November 2023:** Priority Review granted; FDA determines **no AdCom required**

- **March 14, 2024:** FDA approval as Rezdiffra (4 months ahead of PDUFA)

3.3 The “No AdCom” Decision: A Critical Signal

The FDA’s decision to forgo an Advisory Committee meeting was a strong positive signal indicating high confidence in the benefit-risk profile:

3.4 OCA Advisory Committee: The Cautionary Tale

In stark contrast, OCA faced a hostile Advisory Committee meeting on June 22, 2023 (the same day Resmetirom announced positive results):

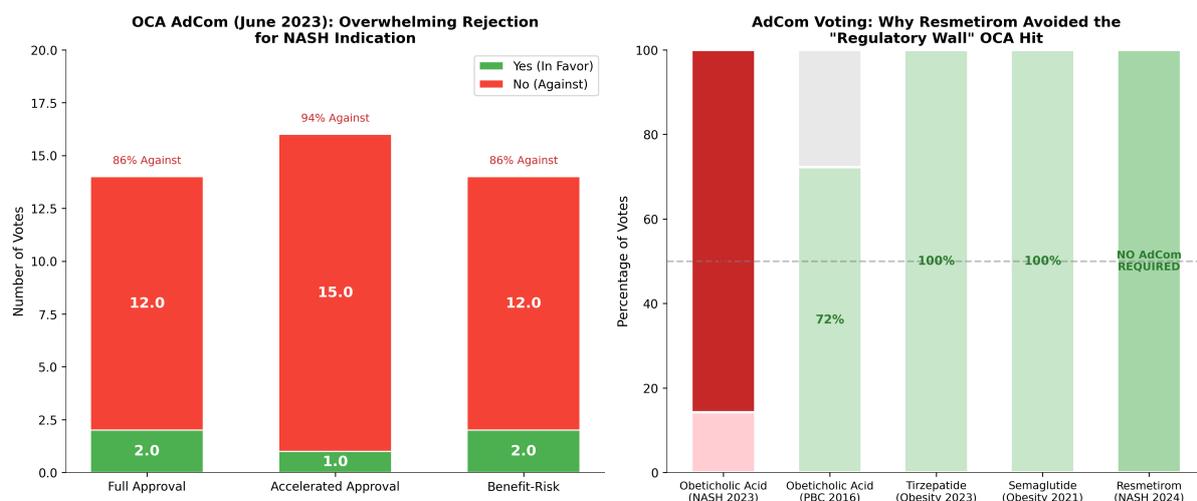


Figure 4: **OCA Advisory Committee Voting Results (June 2023)**. The committee voted overwhelmingly against approval on all key questions, with pruritus and LDL-C elevation cited as primary concerns.

Table 10: OCA Advisory Committee Votes

Question	Yes–No	Result
Full approval based on clinical outcomes?	2–12	Rejected
Accelerated approval based on surrogate?	1–15	Rejected
Acceptable benefit-risk profile?	2–12	Rejected

3.5 Approval Drivers Analysis

A weighted factor analysis reveals why Resmetirom succeeded where OCA failed:

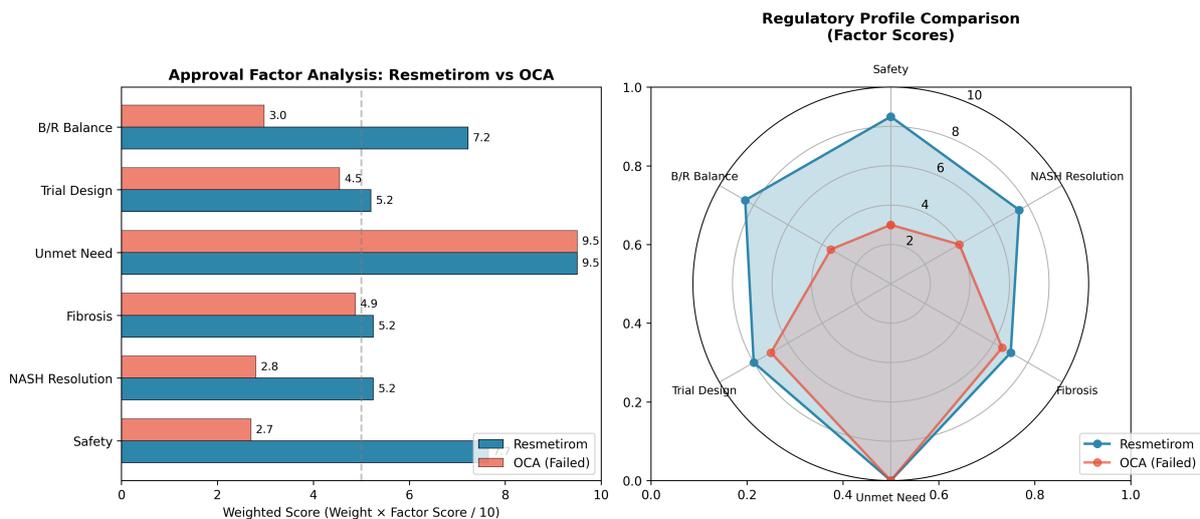


Figure 5: **FDA Approval Drivers: Resmetirom vs. OCA.** Safety profile and benefit-risk balance were the primary differentiators enabling Resmetirom’s approval.

Table 11: Weighted Approval Factor Analysis

Factor	Weight	Resmetirom	OCA
Safety Profile	9.0	8.5	3.5
Unmet Medical Need	9.5	10.0	10.0
Benefit-Risk Balance	8.5	8.5	4.0
Fibrosis Efficacy	7.5	7.0	6.5
NASH Resolution	7.0	7.5	3.5
Trial Design	6.5	8.0	7.0
Weighted Total	–	40.1/48	25.5/48

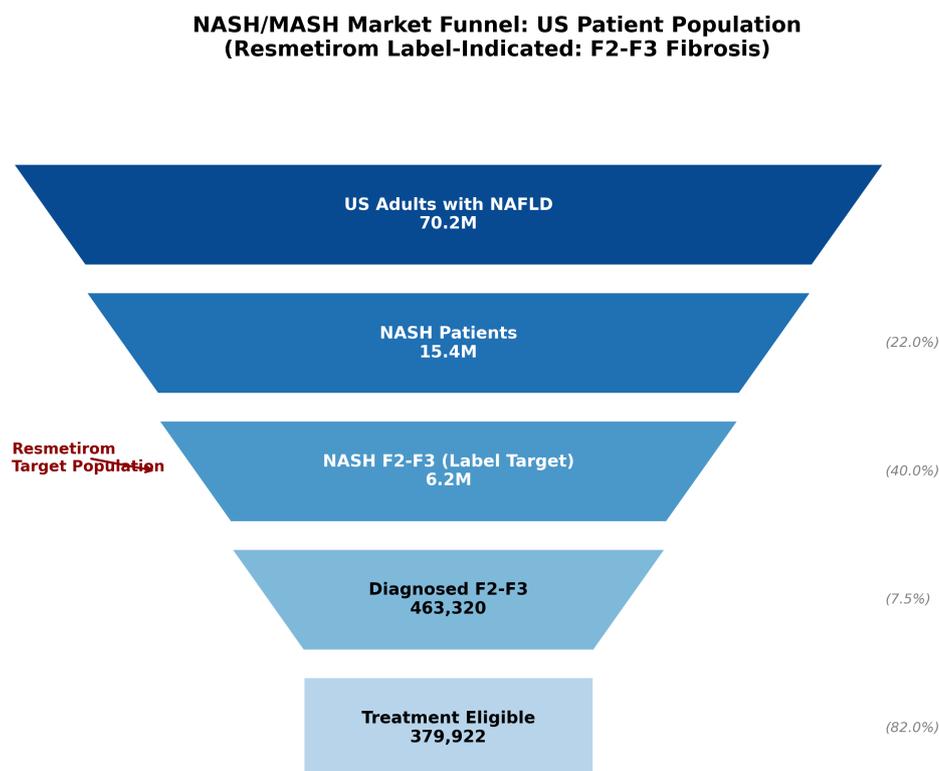
3.6 Accelerated Approval: Post-Marketing Requirements

Resmetirom received **accelerated approval** based on surrogate endpoints (histological improvement). This pathway requires:

4 Commercial Outlook

This section analyzes Resmetirom’s commercial potential, including market sizing, revenue projections, and competitive dynamics with GLP-1 agonists.

4.1 Market Sizing: The NASH Opportunity



Sources: Estes et al. Hepatology 2018; Younossi et al. 2016; Market research estimates

Figure 6: NASH Market Funnel: From Prevalence to Treatable Population. The primary commercial constraint is low diagnosis rates (5–10%), significantly limiting the near-term addressable market.

Table 12: US Addressable Market Analysis

Segment	Population	Diagnosed (%)	Treatable
Total NASH	15,444,000	5%	–
F2 Fibrosis	3,861,000	6%	~80%
F3 Fibrosis	2,316,600	10%	~85%
F2–F3 (Label Target)	6,177,600	7.5%	~380,000

4.2 Pricing Strategy

Table 13: Rezdiffra Pricing

Metric	Value
WAC (List Price)	\$47,400/year
Estimated Net Price (after GTN ~35%)	~\$30,810/year
Launch Positioning	Specialty/hepatology-focused

4.3 Revenue Projections by Scenario

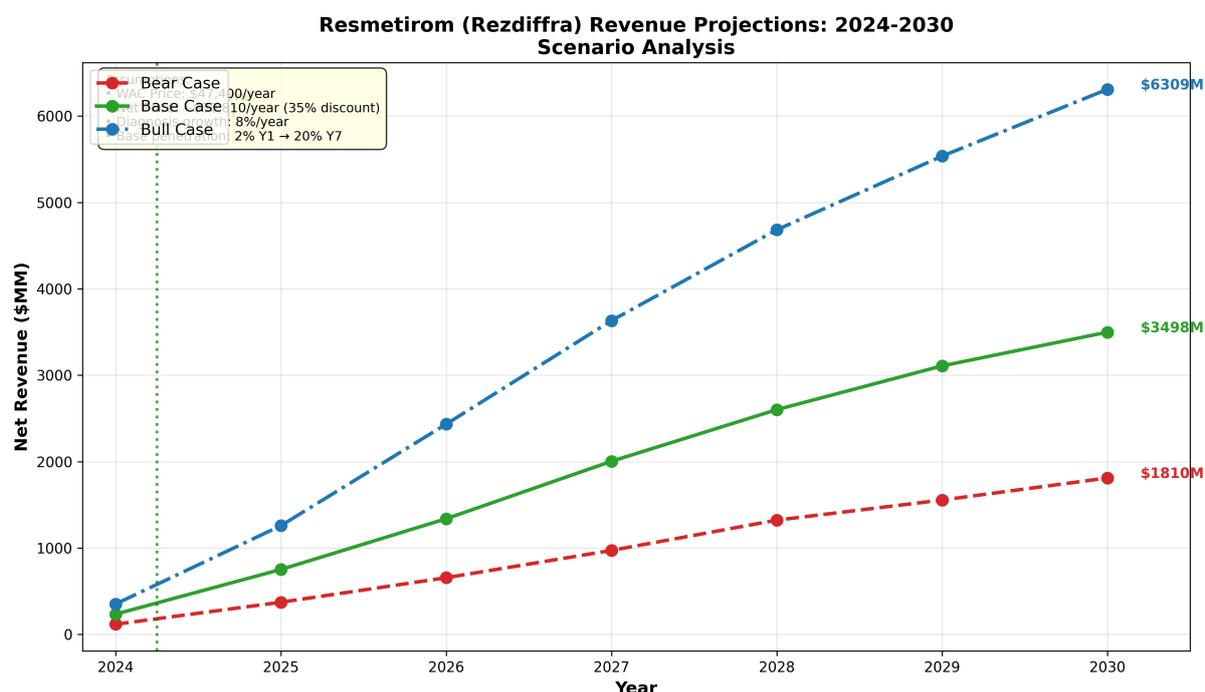


Figure 7: **Rezdiffra Revenue Projections (2024–2030)**. Three scenarios reflecting different assumptions about market penetration, payer dynamics, and competitive pressures from GLP-1 agonists.

Table 14: Net Revenue Projections by Scenario (\$MM)

Year	Bear Case	Base Case	Bull Case
2024	\$117	\$234	\$351
2025	\$372	\$751	\$1,258
2026	\$656	\$1,338	\$2,433
2027	\$972	\$2,003	\$3,631
2028	\$1,322	\$2,601	\$4,683
2029	\$1,555	\$3,108	\$5,535
2030 (Peak)	\$1,810	\$3,498	\$6,309

Scenario Assumptions:

- **Bear Case (11% peak penetration):** Slow adoption due to GLP-1 competition, payer resistance, limited diagnosis expansion
- **Base Case (20% peak penetration):** Moderate adoption with specialty positioning, standard payer coverage
- **Bull Case (35% peak penetration):** Strong differentiation messaging, broad coverage, combination therapy adoption

4.4 Competitive Landscape: The GLP-1 Question

The central commercial question is whether GLP-1 agonists represent a threat or synergy opportunity for Resmetirom.

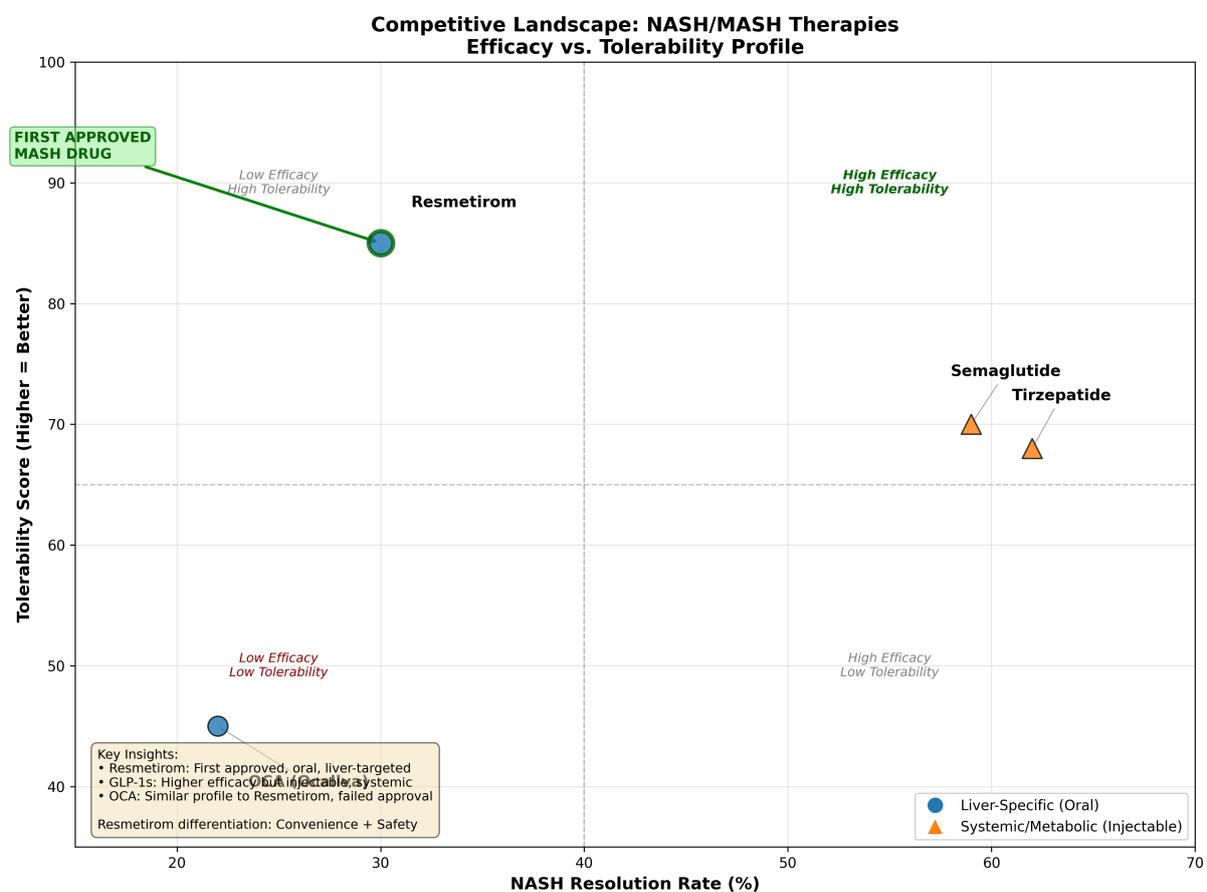


Figure 8: **NASH Competitive Landscape.** Resmetirom holds first-mover advantage as the only approved therapy, while GLP-1s pursue approval with superior efficacy data.

Table 15: Competitive Profile Comparison

Attribute	Resmetirom	Semaglutide	Tirzepatide
Mechanism	THR- β agonist	GLP-1 RA	GIP/GLP-1 RA
Target	Liver-specific	Systemic/metabolic	Systemic/metabolic
Route	Oral (daily)	Injectable (weekly)	Injectable (weekly)
NASH Resolution	30%	59%	62%
Fibrosis Improvement	26%	34%	51%
Weight Loss	Minimal	~15–17%	~20–25%
Tolerability Score	85/100	70/100	68/100
Approval Status	Approved	Phase 3	Phase 3

4.4.1 The GLP-1 “Threat” Argument

1. **Superior Efficacy:** GLP-1s show 2× higher NASH resolution rates
2. **Multiple Benefits:** Weight loss, CV protection, diabetes control
3. **Market Momentum:** Combined GLP-1 sales approaching \$50B annually
4. **Patient Preference:** “One drug for everything” appeal

4.4.2 The GLP-1 “Synergy” Counter-Argument

1. **Different Patient Profiles:**
 - GLP-1s: Obese patients with metabolic syndrome
 - Resmetirom: Non-obese NASH, GLP-1 contraindicated/intolerant patients
2. **Combination Potential:** GLP-1s address systemic dysfunction; Resmetirom provides direct hepatoprotection
3. **Route Preference:** Oral daily vs. injectable weekly appeals to different patients
4. **Liver-Targeted Mechanism:** Direct hepatocyte action vs. indirect GLP-1 effects
5. **First-Mover Advantage:** 2–3 years ahead in market with approved indication

5 Investment Conclusion

5.1 SWOT Analysis

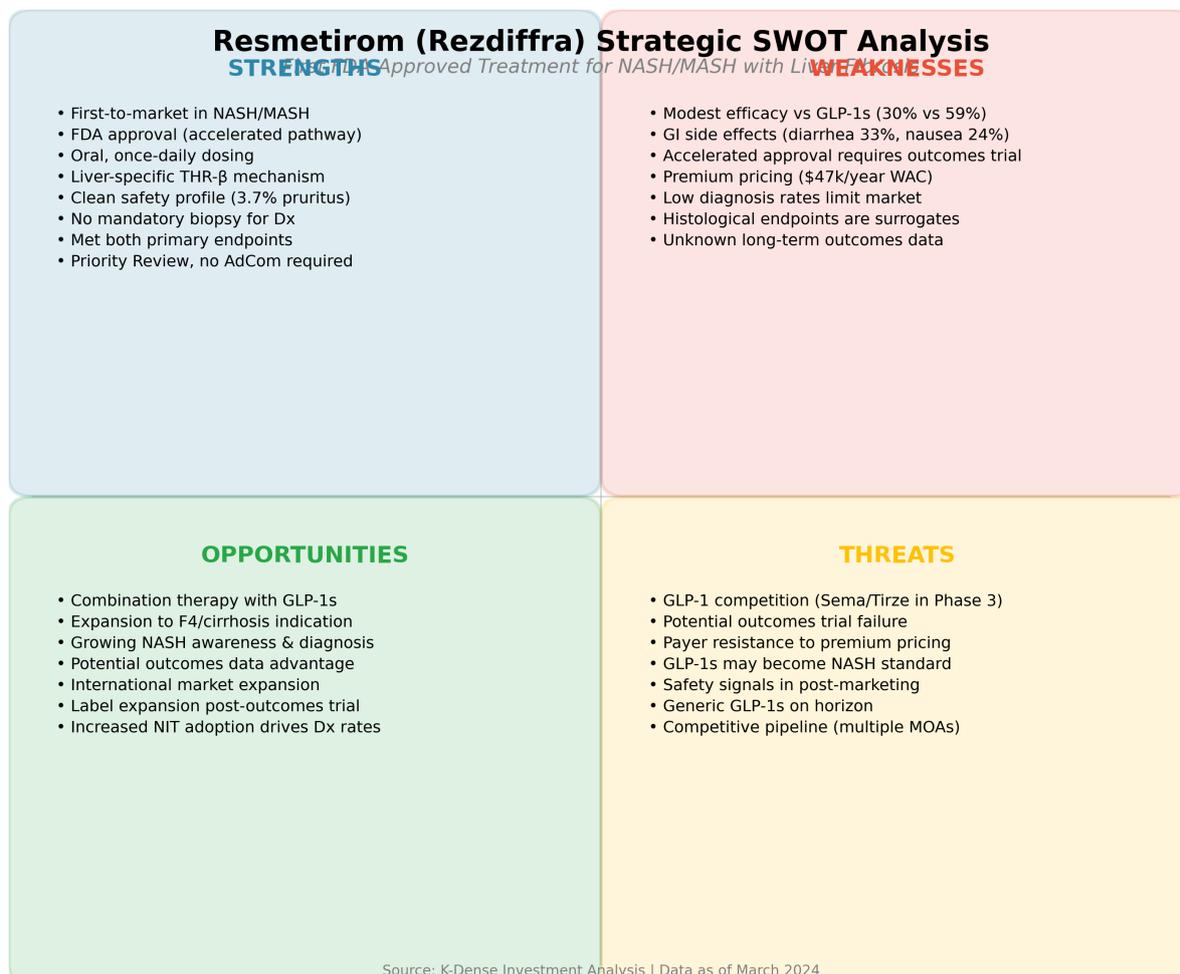


Figure 9: **Rezdiffra Strategic SWOT Analysis.** First-mover advantage and clean safety profile are offset by modest efficacy versus emerging GLP-1 competition.

Table 16: Strategic SWOT Summary

Strengths	Weaknesses
First-in-class, first-to-market	Modest efficacy vs. GLP-1s
Clean safety profile (no pruritus, CV neutral)	GI adverse events (diarrhea, nausea)
Oral administration	Accelerated approval pathway risk
No biopsy requirement (Bull label)	Limited weight loss benefit
Liver-specific mechanism	–
Opportunities	Threats
Combination therapy with GLP-1s	GLP-1 competition (superior efficacy)
Label expansion (F4 cirrhosis, pediatric)	Outcomes trial (MAESTRO-OUTCOMES) risk
Growing NASH diagnosis rates	Pricing pressure, payer restrictions
International expansion	Post-marketing safety surveillance

5.2 Risk Factors

5.2.1 Near-Term Risks

1. **MAESTRO-OUTCOMES Confirmatory Trial:** Required for conversion to full approval; failure could result in accelerated approval withdrawal
2. **GLP-1 Phase 3 Readouts:** Semaglutide (ESSENCE) and Tirzepatide approvals in NASH could compress market share
3. **Payer Dynamics:** Prior authorization requirements, step therapy, and formulary restrictions could limit uptake

5.2.2 Long-Term Risks

1. **Post-Marketing Safety:** Novel signals emerging with broader real-world use
2. **Generic/Biosimilar Competition:** Patent expiration timeline (estimated late 2030s)
3. **Next-Generation Therapies:** Superior efficacy agents in development

5.3 Investment Scenarios

Table 17: Post-Approval Investment Scenario Analysis

Scenario	Key Assumptions	Commercial Outcome	Peak Revenue
Bull Case	Combination standard of care; outcomes trial success; Dx expansion	Dominant franchise; broad adoption	\$6.3B
Base Case	Specialty positioning; GLP-1 coexistence; moderate penetration	Solid hepatology franchise	\$3.5B
Bear Case	GLP-1 dominance; outcomes concerns; payer resistance	Niche positioning	\$1.8B

5.4 Summary Conclusions

5.5 Recommendation

Key Monitoring Points:

- Launch trajectory and early prescription trends
- GLP-1 NASH Phase 3 readouts and approval timelines
- MAESTRO-OUTCOMES interim and final data
- Payer coverage decisions and prior authorization patterns
- Combination therapy clinical data generation

Appendices

A. Data Sources

- Harrison SA, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med.* 2024;390(6):497–509.
- Younossi ZM, et al. Results from the REGENERATE trial of obeticholic acid. *J Hepatol.* 2023.
- GENFIT Press Release. RESOLVE-IT Phase 3 Trial Results. May 2020.
- FDA Approval Letter: Rezdiffra (resmetirom). March 14, 2024.
- FDA Endocrinologic and Metabolic Drugs Advisory Committee Transcripts. June 2023.
- ClinicalTrials.gov: NCT03900429 (MAESTRO-NASH), NCT02548351 (REGENERATE)
- Madrigal Pharmaceuticals SEC Filings and Investor Presentations (2023–2024)
- Estes C, et al. Modeling the epidemic of nonalcoholic fatty liver disease. *Hepatology.* 2018.

B. Glossary of Terms

Term	Definition
NASH	Nonalcoholic Steatohepatitis
MASH	Metabolic dysfunction-Associated Steatohepatitis (new nomenclature)
THR- β	Thyroid Hormone Receptor Beta
FXR	Farnesoid X Receptor
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
AdCom	FDA Advisory Committee
NIT	Non-Invasive Testing
WAC	Wholesale Acquisition Cost
GTN	Gross-to-Net (rebate adjustments)
CRL	Complete Response Letter

C. Methodology Notes

Approval Probability Assessment: Pre-approval probability was assessed using a weighted factor model incorporating safety profile, efficacy magnitude, unmet need, regulatory signals, and historical NASH program outcomes.

Revenue Projections: Three-scenario model based on epidemiological data, diagnosis rate assumptions, market penetration curves, and net pricing estimates. Penetration rates benchmarked against specialty pharmaceutical launch analogues.

Competitive Analysis: Efficacy data from published Phase 3 results and conference presentations. Safety comparisons based on trial adverse event reporting.

*This analysis is for informational purposes only and does not constitute investment advice.
Generated: February 2026*