

PSC Category Definition War: Ipsen Portfolio Defense vs Volixibat Symptom-First Challenger

When a Rival's Weakness Is Also Your Own: What a Rare-Liver
Wargame Reveals About Regulatory Exposure, the Mirror Problem,
and the Bundle Advantage

30 September 2026

AI-Powered Wargame | 4 Scenario Variants | 3 Decision Rounds | 2 Competing
Teams

Executive Summary

In a three-round simulation spanning Q4 2026 to 2028, Ipsen defended its rare-liver franchise against Mirum's volixibat across four regulatory futures.

The central finding is an asymmetry.

Mirum's weighted score ranged from 50.6 to 63.5 across the variants, and its Regulatory Position alone moved 23 points, from 37 to 60.

Ipsen's weighted score moved only 6.6 points, from 55.5 to 62.1.

The regulator set Mirum's range; Ipsen's range was set largely by *its own conduct*. We call this **the Asymmetric Exposure**.

Three results held in every variant. **Ipsen's KOL and Patient Trust finished below its starting value of 55 in all four runs, between 44 and 52**, because its counter-moves kept attacking the safety of IBAT inhibitors, the class that includes Ipsen's own Bylvay. Ipsen's Access Power held at 63 to 64 everywhere, above Mirum's 49 to 56, and payers chose Ipsen's portfolio contracting in the final round of three variants. The hepatology KOL network endorsed a full-spectrum model, pairing symptom relief with disease modification, in 8 of 12 rounds.

Mirum's regulatory path was what diverged.

Under Symptom-First Breakout volixibat was approved in early 2028, Mirum's Category Control reached 69 and Ipsen trailed 55.5 to 63.5.

Under Safety Reset no filing was possible inside the game, Mirum's Regulatory Position fell to 37 and Ipsen led 62.1 to 50.6.

Contested Path ended level, 59.9 to Mirum against 59.2.

Disease-Modification Race gave Ipsen a narrow lead, 60.2 to 58.6, as guidelines moved towards disease-directed therapy.

Ipsen's business development answer split by variant: an evaluation option and then no Phase 3 licensing under Contested Path, combination research under Safety Reset, and talks on US rights to Dr. Falk's norucholic acid under the other two. No deal changed the score inside the window. Portfolio Defense stayed between 69 and 70 in all four runs.

Context

Primary sclerosing cholangitis has no approved therapy in the US, EU or UK. Mirum's Phase 2b VISTAS study of volixibat met its primary endpoint in 2026: a 1.64-point placebo-adjusted improvement on the Adult ItchRO scale, with 56% of moderate-to-severe patients achieving at least a two-point reduction against 26% on placebo. Discontinuations for adverse events were 9.1% against 2.5%, and liver-test elevations were more frequent. In August 2026 FDA granted volixibat Breakthrough and Orphan designations but recommended a Phase 3 study; Mirum targets a possible NDA in H1 2027. Linerixibat, now licensed worldwide to Alfasigma, was approved for PBC itch in the US in March 2026 and received a positive CHMP opinion in July.

Ipsen markets Iqirvo in PBC and Bylvay, itself an IBAT inhibitor with liver-monitoring warnings, in pediatric cholestasis. Its elafibranor PSC Phase 3, ELASCOPE, uses event-free survival over roughly five years, so it will not read out in the game window. In 2026 Ipsen's BOLD study of odevixibat in biliary atresia missed its primary endpoint, and its own IBAT-class PSC study, ritivixibat, ended early with no further PSC studies planned.

Dr. Falk's norucholic acid has positive Phase 3 data in PSC and a NICE appraisal scheduled for January 2027; Chemomab has agreed a merger that puts nebokitug's PSC Phase 3 on hold pending a partner.

Simulation design

Teams / players

Ipsen Rare-Liver Portfolio Defense was the user AI team, played by a Rare-Liver General Manager, a Clinical Development Lead, a Market Access and HTA Lead, and a Business Development and External Innovation Lead.

Mirum Symptom-First Challenger Coalition was the AI competitor, played by a Strategy Lead, a Volixibat Regulatory Lead, a Medical Affairs and KOL Lead, and a Commercial and Access Lead.

Five stakeholder panels adjudicated each round: a Regulator Panel, a Payer and HTA Consortium, a Hepatology and PSC KOL Network, a PSC Patient Advocacy Coalition, and an Adjacent Competitor Watch.

Four variants fixed the external events in each round. These events are scenario assumptions describing a hypothetical future, not reported news.

Contested Path had FDA accept a VISTAS-based NDA with a parallel Phase 3 and move to label negotiation.

Safety Reset had FDA require a completed Phase 3 and a larger safety database, so no filing was possible within the game.

Symptom-First Breakout had FDA accept VISTAS, grant priority review and approve volixibat in early 2028.

Disease-Modification Race had norucholic acid win a positive CHMP opinion and guidelines make disease-directed therapy the foundation of care.

Rounds and key questions

Round 1 (Q4 2026) asked how Ipsen should engage on safety and evidence standards, given FDA's Phase 3 recommendation, without appearing to dismiss the burden of severe pruritus.

Round 2 (H1 2027) asked whether Ipsen could shift the market from 'first symptom therapy wins' to 'durable rare-liver leadership requires disease modification, safety and portfolio breadth'.

Round 3 (H2 2027 to 2028) asked for Ipsen's best endgame: defend with access and evidence, reposition around elafibranor's Phase 3, pursue external innovation, or rethink odevixibat's adult role after BOLD.

Adjudication rubric (weighted KPIs)

Six KPIs were scored from 0 to 100: Category Control (weight 5), Evidence Strength (5), Regulatory Position (4), Access Power (4), Portfolio Defense (3) and KOL and Patient Trust (3). Ipsen started at 55, 58, 52, 60, 64 and 55; Mirum at 58, 62, 45, 50, 50 and 62. Weighted starting scores were 57.1 for Ipsen and 54.8 for Mirum.

Wargame overview

PSC Category Definition War: Ipsen Rare-Liver Portfolio Defense vs Mirum's volixibat · 3 rounds · 4 variants

Rounds and key questions	ROUND 1 Q4 2026	ROUND 2 H1 2027	ROUND 3 H2 2027 ~ 2028
Each round is one decision cycle for both teams. The question is what the round asks of Ipsen.	How should Ipsen engage on safety and evidence standards, after FDA's Phase 3 request, without dismissing the burden of severe itch?	Can Ipsen shift the market from 'first symptom therapy wins' to 'durable leadership needs disease modification, safety and portfolio breadth'?	What is Ipsen's best endgame: defend access and evidence, reposition around ELASCOPE, pursue external innovation, or rethink odevixibat?
SCENARIO VARIANTS · what is assumed to happen in each round			
Contested Path Filing accepted with a parallel Phase 3; no side wins the category.	● Filing basis negotiated under Breakthrough status	● NDA accepted for standard review, with liver-monitoring label conditions	● FDA decision pending; label under negotiation
Safety Reset FDA holds to its Phase 3 request; volixibat cannot be approved inside the game.	● Phase 3 and a larger liver-safety database required before filing	● Phase 3 starts; FDA raises a liver-safety query	● No NDA possible inside the game window
Symptom-First Breakout Severe PSC itch becomes a branded, independently treated category.	● FDA accepts a VISTAS-based filing, Phase 3 post-approval	● Priority review; VANTAGE PBC positive; Lynavoy approved in EU	● Volixibat approved in the US (early 2028)
Disease-Modification Race Disease-directed therapy becomes the foundation of PSC care.	● Norucholic acid under EU review; FDA Phase 3 request stands	● Positive CHMP opinion for norucholic acid; Mirum starts Phase 3	● Guidelines: disease-directed base, itch drugs as add-ons; Mirum files

Variant events are scenario assumptions describing a hypothetical future, not reported news.

Wargame conducted using LucidWargames (www.lucidwargames.com), LucidQuest's AI-powered competitive simulation platform

What happened: the regulator set Mirum's range, Ipsen's conduct set its own

Act I: The regulator follows the script, and Ipsen's field force does not

All events described below are scenario assumptions within each variant.

In Round 1 the Regulator Panel accepted a filing with enhanced monitoring under Contested Path and Symptom-First Breakout, and required a Phase 3 before any filing under Safety Reset and Disease-Modification Race. Each decision matched its variant, and none was reversed later. Payers imposed an off-label step edit in three runs and accepted functional burden evidence under Symptom-First Breakout.

Ipsen's primary moves were constructive. It proposed a dual-goal treatment framework, funded burden-of-illness registries with patient groups and convened consensus panels on liver monitoring. Its counter-moves told a different story. In all four runs Ipsen challenged IBAT class toxicity or the GI risks of volixibat in patients with IBD. Trust fell below 55 in every run by the end of the round. This is **the Mirror Problem**: Bylvay is itself an IBAT inhibitor with liver-monitoring warnings, so *an attack on the class is an attack on Ipsen*.

Act II: The paths fork, and payers ask for two keys

By Round 2 the four worlds had separated.

Under Contested Path FDA accepted the NDA for standard review and limited use to patients without cirrhosis or with compensated cirrhosis.

Under Safety Reset Mirum started its Phase 3 and answered an FDA information request with a blinded hepatic safety committee.

Under Symptom-First Breakout priority review was granted, VANTAGE PBC read out positively and linerixibat was approved in the EU.

Under Disease-Modification Race norucholic acid received a positive CHMP opinion and Mirum began its Phase 3.

Payers accepted sleep and functional evidence as a basis for branded coverage in three of four variants, and kept a generic step edit in the fourth.

Across the game every variant used both levers at least once. This is **the Two-Key Rule**: access required a documented generic failure *and* functional evidence, never one alone.

Ipsen's counter-moves crossed the line again. Under Safety Reset it claimed a 'streamlined profile' against Mirum's monitoring burden and was reprimanded by hepatologists and advocates. Trust fell in Round 2 in every run.

Act III: Four end states, and an Ipsen endgame that split

Under Symptom-First Breakout FDA approved volixibat in early 2028 and Mirum launched through its Livmarli field force with week-4 value-based contracts. Advocates repudiated Ipsen's description of itch relief as 'transient symptom masking', and Ipsen's trust fell to 44.

Under Contested Path the label was concluded with monthly then quarterly liver tests, and Alfasigma's linerixibat rollout capped IBAT pricing.

Under Safety Reset no NDA could be filed in the game window.

Under Disease-Modification Race FDA accepted Mirum's NDA for priority review with a risk management plan, and draft guidance positioned IBAT drugs as monitored add-ons.

Two patterns stand out in the final round.

First, payers chose Ipsen's multi-product contracting under Safety Reset, Symptom-First Breakout and Disease-Modification Race; this is **the Bundle Advantage**.

Second, Ipsen's trust recovered only where it stopped attacking: from 49 to 52 under Safety Reset, where it defended the class, and from 49 to 51 under Disease-Modification Race, where its main moves avoided safety attacks.

Ipsen's endgame did not converge. It took an evaluation option on nebokitug and then rejected Phase 3 licensing under Contested Path, favoured combination research under Safety Reset, and opened talks on US rights to norucholic acid under the other two.

The KOL network endorsed **the Full-Spectrum Settlement** in 8 of 12 rounds and rejected claims that itch relief itself modifies disease.

Ipsen finished between 55.5 and 62.1 weighted. Access Power was 63 to 64 and Portfolio Defense 69 to 70 in every run. Category Control ranged from 47 to 64 and Regulatory Position from 50 to 58. KOL and Patient Trust ranged from 44 to 52, below baseline everywhere.

Mirum finished between 50.6 and 63.5 weighted. Regulatory Position ranged from 37 to 60 and Category Control from 49 to 69. KOL and Patient Trust ranged from 61 to 71, at or above baseline in every variant except Safety Reset.

The regulator decided how far Mirum could go. Ipsen's own field force decided how much *trust* it kept.

Key takeaways

Ipsen's exposure is reputational, not regulatory.

Across four regulatory paths Ipsen's weighted score moved 6.6 points and Mirum's 12.9, with Mirum's Regulatory Position alone swinging 23. Ipsen cannot control volixibat's approval and gained little from trying. The one KPI it lost everywhere, KOL and Patient Trust, was lost through its own counter-moves.

Attacking the IBAT class means attacking Bylvay.

This is **the Mirror Problem**. Ipsen markets an IBAT inhibitor with the same liver-monitoring warnings it tried to use against volixibat. Stakeholders noticed: a 'streamlined profile' claim drew reprimands under Safety Reset, and trust ended below baseline in every run. Trust recovered only in the two rounds where Ipsen stopped attacking the class.

Portfolio contracting is Ipsen's strongest lever.

Payers chose Ipsen's multi-product contracts in the final round of three variants, including Symptom-First Breakout, where volixibat was approved. Ipsen's Access Power held at 63 to 64 in every world, above Mirum's 49 to 56. *Competing on access, not on a rival's side effects*, is where Ipsen's position is most robust.

Payers hold two keys, and turn both.

Every variant kept an off-label step edit and every variant accepted functional evidence at some point. Mirum's route through was a value-based contract tied to itch and sleep response at week 4; Ipsen's attempts to gate itch relief on biochemical markers were rejected. Neither blanket access nor blanket restriction survived.

The category settles as full-spectrum, not symptom-first or disease-first.

KOLs backed the full-spectrum model in 8 of 12 rounds. Even after approval they refused to accept that itch relief modifies disease, and even under disease-directed guidelines they kept itch relief as an urgent need. The winning position is to be credible on both pillars, which Ipsen cannot yet do in adult PSC after stopping ritivixibat.

No deal moved the needle inside the window.

Left to decide for itself, Ipsen chose different external strategies in each world, from declining Phase 3 licensing to pursuing US rights to norucholic acid. Portfolio Defense stayed at 69 to 70 regardless. External innovation looks necessary for the 2030s, but inside 2028 *conduct and contracting* did more for Ipsen than any transaction.

Open questions to pressure-test next

How much monitoring burden does it take to cancel out the value of itch relief for payers? Payers in the Safety Reset world weighed liver and GI surveillance costs against symptom benefit. Quantifying that trade-off would show whether monitoring is a real access barrier or only a talking point.

Can Ipsen rebuild trust with patient groups without appearing to trade on their suffering? Trust was Ipsen's weakest KPI in every run. Testing a variant where Ipsen's field force never raises class safety would show how much of the gap is recoverable and how quickly.

Would Dr. Falk license US rights to norucholic acid, and on what terms? Ipsen opened talks in two variants, but the simulation did not test the counterparty. A deal-focused run would show whether this is a realistic bridge to ELASCOPE or a strategic assumption.

Which non-invasive markers could bridge the evidence gap before ELASCOPE reads out? Ipsen proposed interim ALP, ELF and elastography sub-studies in several runs. Knowing whether regulators and HTA bodies would accept any of them would change the value of Ipsen's disease-modification narrative before 2030.

How do patients with PSC and IBD weigh itch relief against GI side effects? Both teams argued about diarrhoea and IBD flares in this group, which is 60 to 80% of patients. Direct preference evidence would settle an argument the simulation could only stage.

Methodology note

The simulation ran three decision rounds, representing Q4 2026, H1 2027 and H2 2027 to 2028, across four variants: Contested Path, Safety Reset, Symptom-First Breakout and Disease-Modification Race.

Two teams competed: Ipsen Rare-Liver Portfolio Defense (user) and Mirum Symptom-First Challenger Coalition (AI).

Each round was scored on six weighted KPIs: Category Control, Evidence Strength, Regulatory Position, Access Power, Portfolio Defense, and KOL and Patient Trust.

Five stakeholder panels adjudicated: the Regulator Panel, the Payer and HTA Consortium, the Hepatology and PSC KOL Network, the PSC Patient Advocacy Coalition, and the Adjacent Competitor Watch.

The run was set to the US. The evidence base of 37 data points was verified against public sources as of 30 September 2026. Standalone injects were

switched off; external events were written into each variant as round-specific scenario assumptions, which describe hypothetical futures rather than reported news.

No agent was pointed towards any specific business development target.

Each variant ran once, so differences smaller than about five points should be read with caution.

The output reflects patterns and strategic dynamics, not predictions. It is designed to stress-test assumptions and surface decision-relevant tensions rather than forecast specific market outcomes.