



Original article

Tolibrutinib liver safety: A detailed overview

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ABSTRACT

Tolibrutinib is an oral brain-penetrant Bruton's tyrosine kinase inhibitor thought to modulate persistent maladaptive immune activation within the CNS. It was evaluated in four Phase 3 trials and an open-label long-term safety extension across multiple sclerosis (MS) phenotypes: relapsing MS (RMS; GEMINI 1&2), non-relapsing secondary progressive MS (nrSPMS; HERCULES), and primary progressive MS (PPMS; PERSEUS), with 2958 participants exposed overall. Tolibrutinib reduced disability progression by 31% in nrSPMS and 29% in RMS but showed no meaningful benefit in PERSEUS. During clinical development, drug-induced liver injury (DILI) emerged as an important identified risk of tolibrutinib exposure. A total of 139 (4.7%) of the 2958 tolibrutinib-exposed participants experienced ALT elevations $>3 \times \text{ULN}$, including 49 (1.66%) with elevations $>8 \times \text{ULN}$ and 17 (0.57%) $>20 \times \text{ULN}$. Six (0.20%) cases met Hy's Law criteria predictive of serious liver injury. All cases occurred within the first 90 days of exposure and resolved without sequelae except one participant who required a liver transplant and died from postoperative complications. Only one of the Hy's Law cases occurred among the 920 participants (0.11%) exposed following implementation of enhanced liver test monitoring. Weekly liver test monitoring for 12 weeks enabled earlier detection of elevated ALT (40 vs 60 days) and earlier recovery (44 vs 57 days) compared to less frequent monitoring. Mechanistic studies using liver spheroids showed no evidence of direct hepatocellular toxicity, supporting an idiosyncratic mechanism. This overview summarizes tolibrutinib liver safety data, characterizes DILI cases, describes mechanistic and biomarker findings, and demonstrates the impact of enhanced monitoring on early detection and risk mitigation.

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1. Introduction

1.1. Tolibrutinib: mechanism and clinical development

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disorder of the central nervous system (CNS) leading to permanent loss of neurological function. Thirty years of drug development have delivered >20 approved therapies that are very effective at halting new lesion formation and preventing relapses (Yang et al., 2022). However, it has also become increasingly apparent that the existing treatments have limited efficacy in slowing disability accumulation, with "Progression Independent of Relapse Activity" (PIRA) becoming the focus of next-generation drug development in MS to meet the remaining unmet

need (Kappos et al., 2020; Giovannoni et al., 2022; Scalfari et al., 2024). Secondary progressive MS (SPMS) without relapses represents a stage of the disease where neurological disability has accumulated and steadily worsens independent of relapses, yet there are limited treatment options available to slow or halt this progression.

Bruton's tyrosine kinase (BTK) has emerged as a promising therapeutic target due to its role in modulating disease-associated microglia and B cells thought to participate in persistent neuroinflammation that drives disability accumulation (Krämer et al., 2023; Gruber et al., 2024).

Tolibrutinib is an oral, brain-penetrant BTK inhibitor that was evaluated across the MS spectrum in four Phase 3 clinical trials: GEMINI 1 [NCT04410978] and GEMINI 2 [NCT04410991] in relapsing MS (RMS), HERCULES [NCT04411641] in non-relapsing secondary

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progressive MS (nrSPMS), and PERSEUS [NCT04458051] in primary progressive MS (PPMS). A total of 2958 participants were exposed to tolebrutinib across core studies and open-label long-term safety extensions. In these pivotal trials, tolebrutinib treatment significantly reduced the risk of confirmed disability progression by 31% relative to placebo in nrSPMS (Fox et al., 2025) and nominally reduced the risk by 29% relative to teriflunomide in RMS (Oh et al., 2025) while a non-significant risk reduction of 14% was observed in the PPMS population studied (Reich et al., 2026).

1.2. Regulatory history

During the Phase 3 program, an important safety signal for drug-induced liver injury (DILI) including cases meeting Hy's Law was identified. As a consequence, the United States Food and Drug Administration (FDA) imposed a partial clinical hold on tolebrutinib in June 2022, halting new enrollment in the United States and suspending dosing for participants with ≤ 60 days of exposure (Sanofi, 2022). The hold was partially lifted in October 2023 for the PPMS and nrSPMS indications but remains in place for RMS patients. Subsequently, other BTK inhibitors (orelabinib [InnoCare, 2022], evobrutinib [Merck, 2023], fenebrutinib [Genentech, 2023]) were subjected to similar holds due to DILI risk. In March 2024, the FDA mandated hepatotoxicity warnings for all approved BTK inhibitors, underscoring the importance of liver safety monitoring across this drug class, including those in development for MS. In December 2025, the FDA issued a complete response letter for the new drug application of tolebrutinib to treat nrSPMS in adult patients, citing severe liver injury risk including cases of Hy's Law as a main concern (FDA, 2025).

1.2.1. Hy's law explained

The concept of Hy's Law originates from the work of Dr. Hyman Zimmerman, a renowned hepatologist and researcher in the field of DILI. His central observation subsequently codified as "Hy's Law" (Cohen and Lewis, 2025) describes the finding that individuals who develop hepatocellular DILI with jaundice face a 10–50% risk of mortality or need for liver transplant. As characterized by the FDA for use in clinical trials and drug development for identifying hepatotoxic drugs capable of severe liver injury, DILI meeting Hy's Law criteria is defined as alanine aminotransferase (ALT) levels $>3 \times$ upper limit of normal (ULN) and concurrent total bilirubin (TBILI) $>2 \times$ ULN after excluding other potential causes (FDA, 2009).

The identification of even one or two Hy's Law cases during clinical trials is regarded by regulatory authorities as a significant hepatotoxicity signal, which has historically resulted in the cessation of further development or the withdrawal of marketing authorization, as exemplified by troglitazone and trovafloxacin (Temple, 2006). Consequently, Hy's Law cases observed in late-stage trials are used to estimate the post-marketing risk of severe DILI. In large global DILI registries, hepatocellular DILI with jaundice is associated with an approximately 10–13% case fatality rate, consistent with Zimmerman's original observation (Andrade et al., 2005; Björnsson and Olsson, 2005; Chalasani et al., 2015).

Notwithstanding these regulatory precedents, several drugs that incurred Hy's Law during development have successfully implemented a Risk Evaluation and Mitigation Strategy (REMS) program to ensure the safe use of a drug where the benefits outweigh the risks, including the risk of DILI. Agents such as tolvaptan (Lohrmann et al., 2025) and pexidartinib (Waheed Rajper et al., 2025) serve as models for how treatments with clinically meaningful benefits for people with significant unmet medical needs can be managed with REMS programs in the context of a rare but serious risk of DILI. These examples illustrate that a well-characterized safety profile, coupled with robust risk minimization measures, can support regulatory approval and enable access to therapies that address critical gaps in the treatment landscape.

1.3. Nonclinical safety assessments and clinical pharmacovigilance

Nonclinical safety studies in mice, rats, rabbits, and dogs identified no evidence of liver injury following repeated supra-pharmacological doses of tolebrutinib (Sanofi data on file). While isolated reports of DILI associated with BTK inhibitors existed in hematology and oncology for structurally and mechanistically similar drugs such as ibrutinib (Tafesh et al., 2019), the IMBRUVICA® (ibrutinib) Warnings and Precautions in Prescribing Information included only general language regarding hepatotoxicity at the time of early tolebrutinib development.

During the tolebrutinib clinical development program design, elevated liver enzymes were defined as an Adverse Event of Special Interest (AESI). Specifically, ALT $>3 \times$ ULN and TBILI $>2 \times$ ULN were monitored based on: (1) case reports associated with other BTK inhibitors (Tafesh et al., 2019; Atallah et al., 2021), (2) data from the evobrutinib Phase 2 MS trial (Montalban et al., 2019), and (3) the known increased risk of liver injury in patients with MS (Tremlett et al., 2006). Monthly assessment of liver enzymes was incorporated at the Phase 2b stage (Reich et al., 2021, Online Supplement) and continued through the Phase 3 program, both to monitor this risk and to adhere to the liver monitoring requirements of teriflunomide, the active comparator in the Phase 3 GEMINI trials.

Early clinical development showed no evidence of significant liver injury in the Phase 1 (N = 40) (Owens et al., 2022) and Phase 2b (N = 130) trials (Reich et al., 2021). However, DILI emerged as an identified risk during the Phase 3 program, after 1960 MS participants had been exposed to tolebrutinib as of June 30, 2022 (Oh et al., 2025; Fox et al., 2025).

1.4. Assessing liver injury in the tolebrutinib clinical development program

Following the identification of DILI as a serious risk during the Phase 3 program, an extensive analysis of safety data to date was undertaken to characterize the pattern of liver injury and the assessments continued for all ongoing trials. A hepatologist was added to the independent Data Monitoring Committee responsible for trial safety oversight. Additionally, an ad hoc Hepatology Assessment Committee (HAC), comprising three independent hepatologists, was convened to review cases of liver injury and advise on patterns and risk mitigation. The following sections summarize these findings, presenting data categorized by the degree of ALT elevation.

One of the key findings of this analysis was that the DILI risk was time-delimited, with the greatest risk occurring within the first 90 days of tolebrutinib exposure. Most cases were mild and reversible upon discontinuation of tolebrutinib.

2. Drug-induced liver injury during tolebrutinib clinical development

2.1. Assessment and adjudication of severe liver enzyme elevations

In the Phase 3 clinical development program, 4.7% of the 2958 tolebrutinib-exposed participants experienced ALT elevations $>3 \times$ ULN of which 1.66% had elevations $>8 \times$ ULN and 0.57% $>20 \times$ ULN (Fig. 1). The 2958 participants include 830 from HERCULES, 933 from GEMINI 1 and 2567 from PERSEUS and 628 from the open-label long-term safety extension (LTS17043) as of the 20 January 2026 cut-off date.

The typical injury pattern of liver test elevations in tolebrutinib-associated DILI is characterized by a rise in ALT and aspartate aminotransferase (AST), with peak elevations occurring within 4–8 weeks of treatment initiation, followed by gradual normalization upon drug discontinuation (Fig. 2). The ALT elevations typically exceeded AST elevations, which were seen concurrently, whereas alkaline phosphatase (ALP) remained relatively stable in most cases. Bilirubin elevations, when present, typically occurred after the aminotransferases peaked and resolved more slowly.

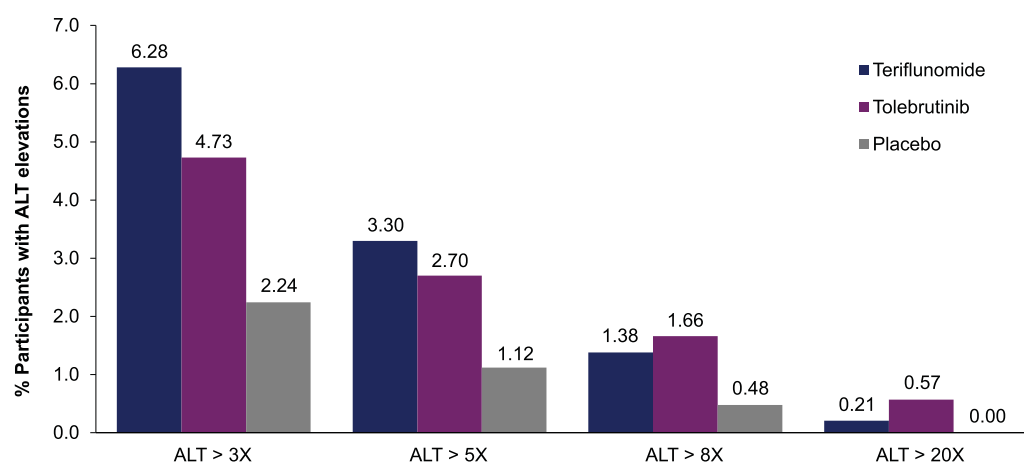


Fig. 1. ALT elevations in the tolebrutinib Phase 3 clinical development program.

Proportion of Phase 3 study participants experiencing ALT elevations at various thresholds (>3 ×, >5 ×, >8 ×, and >20 × ULN). N = 2958 Tolebrutinib; N = 939 Teriflunomide; N = 626 Placebo.

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal.

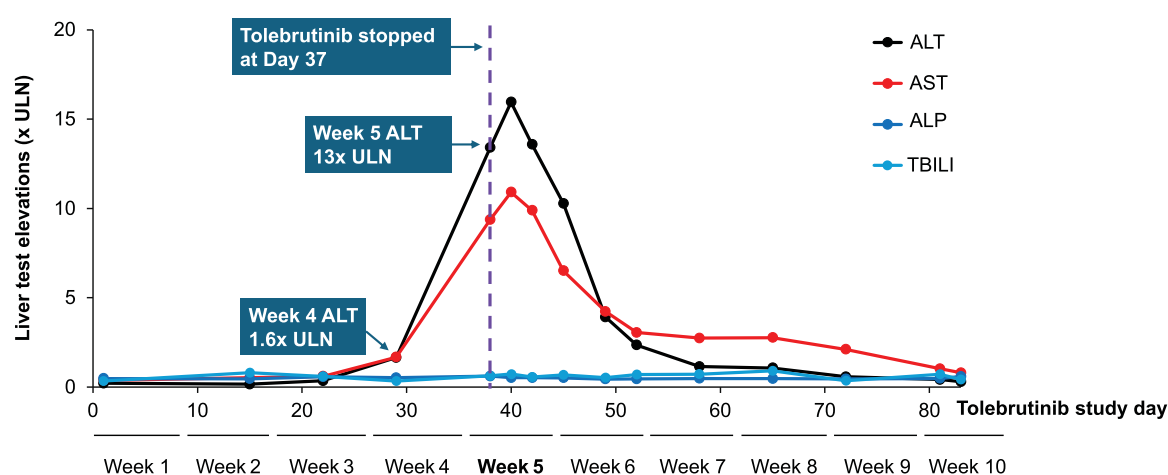


Fig. 2. Illustrative pattern of liver test elevations highlighting the importance of adhering to the frequent monitoring requirements.

Liver test elevations (× ULN) from treatment initiation through peak elevation and recovery in a representative tolebrutinib-treated participant experiencing DILI. Tolebrutinib was discontinued on Day 37 (dashed vertical blue line) following detection of ALT elevation. At Week 4 (Day 29), ALT was 1.6 × ULN; by Week 5 (Day 37), ALT had risen to 13.0 × ULN, illustrating the rapid progression of liver enzyme elevations. Following drug discontinuation, ALT peaked at 16.0 × ULN on Day 40 and subsequently declined, returning to near-baseline levels by Day 58. AST followed a similar trajectory, peaking at 10.9 × ULN on Day 40. ALP remained stable and below the ULN throughout the observation period. Total bilirubin did not exceed the ULN at any time point, consistent with a hepatocellular injury pattern without progression to Hy's Law criteria. Time to peak typically mirrors time to recovery.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBILI, total bilirubin; ULN, upper limit of normal.

Cases of ALT >8 × ULN, or ALT >3 × ULN with concurrent TBILI elevation >2 × ULN (biochemical Hy's Law), were reviewed by the HAC in a blinded manner to assess relatedness to tolebrutinib (categorized as probably, possibly, or unlikely related) and to confirm whether Hy's Law criteria were met unaccompanied by other identifiable causes such as viral hepatitis, cholecystitis, and biliary obstruction.

In the Phase 3 trials, 35 participants (1.2% of the total participants) experienced ALT increases >8 × ULN, assessed as possibly (18 participants) or probably (17 participants) related to tolebrutinib by the HAC. Of these, 17 (0.57%) experienced peak ALT increases of >20 × ULN. Six participants (0.20%) had a concurrent TBILI increase >2 × ULN with no other identifiable cause, thereby meeting Hy's Law criteria (Table 1).

Case descriptions for the 6 Hy's Law cases:

Case #1. Participant enrolled in GEMINI 2 trial with monthly liver test monitoring

Participant with RMS presented on Day 49 with complaints of mild nausea, mild scleral icterus, and ALT 17.9 × ULN, AST 8.4 × ULN (peak

values), and TBILI 7.5 × ULN, which later peaked on Day 52 at 10.6 × ULN. Tolebrutinib was permanently discontinued on Day 49, and the participant was managed as an outpatient (not hospitalized) with liver tests monitored frequently until values normalized on Day 79 (ALT) and Day 147 (TBILI), respectively. Potentially confounding factors include elevated iron panel (serum iron 1.94 × ULN, ferritin 4.9 × ULN), mild iron overload on imaging, and mutation of the homeostatic iron regulator gene (C282Y carrier status). Transferrin saturation on Day 59 exceeded the upper limit of the assay range, and a repeated measurement on Day 79 was elevated at 66%. This event was assessed as probably related to tolebrutinib by the HAC.

Case #2. Participant enrolled in HERCULES trial with monthly liver test monitoring

Participant with SPMS who self-discontinued tolebrutinib on Day 47 due to asthenia and mild jaundice presented on Day 54 with ALT 51.1 × ULN, AST 30 × ULN, and TBILI 5.4 × ULN. Transaminases peaked on Day 57: ALT 65.7 × ULN, and AST 31.5 × ULN; TBILI peaked

Table 1Tolerbrutinib-treated participants having ALT $>3 \times$ ULN with concurrent TBILI $>2 \times$ ULN events assessed by the HAC as meeting Hy's Law criteria.

Trial name	HAC assessment	Monitoring at enrollment and time of detection	Time to onset (Study Day) ^a	Time to recovery (Study Day) ^b	Symptoms	Peak ALT AST TBILI ($\times$ ULN) {INR}	Potential confounders
Case #1 GEMINI 2 NCT04410991	Probably related	Monthly testing Event Detected Month 2	49	30	Mild nausea, mucosal cutaneous jaundice, choloria, light-colored stools	17.9 8.4 10.6 {INR WNL}	Iron overload / genetic predisposition for iron overload; elevated iron panel and TSAT
Case #2 HERCULES NCT04411641	Probably related	Monthly testing Event Detected Month 2	54	66	Jaundice and increased asthenia	65.7 31.5 10.0 {INR WNL}	None to date
Case #3 GEMINI 1 NCT04410978	Possibly related	Monthly testing Event Detected Month 2	57	52	Nausea	98.7 49.4 13.7 {INR 1.6}	Elevated baseline ALT ($1.7 \times$ ULN) Elevated iron panel parameters Alcohol
Case #4 PERSEUS NCT04458051	Possibly related	Monthly testing Event Detected Month 3	85	41	Nausea and vomiting	25.7 25.4 2.7 {INR WNL}	Previous hepatic laboratory abnormalities secondary to NSAIDs and PPIs, ursodiol, COVID-19 booster (Spikevax/Moderna Day 63)
Case #5 HERCULES NCT04411641	Probably related	Biweekly testing Event Detected Week 6	44	Not recovered / fatal	Jaundice, nausea, vomiting, right upper quadrant tenderness	65.0 49.5 31.4 {INR 3.7}	Obesity
Case #6 Long-term safety NCT06372145 (teriflunomide arm in GEMINI)	Possibly related	Weekly testing Event Detected Week 4	29	25	Fatigue	60.3 34.8 3.3 {INR WNL}	"Tong ren tang fish maw" pills (Days 27–28), Isolated GGT elevation, Obesity

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; GGT, gamma-glutamyl transferase; HAC, Hepatology Assessment Committee; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; TSAT, transferrin saturation; TBILI, total bilirubin; ULN, upper limit of normal; WNL, within normal limits.

^a Time to onset defined as the Study Day at which ALT $>3 \times$ ULN.

^b Time to recovery defined as time from drug interruption to ALT $<1.5 \times$ ULN.

on Day 51 ($10.0 \times$ ULN). The participant did not require hospitalization and liver tests were monitored frequently until they normalized on Day 113. No confounding factors were identified in this case. As this participant had a negative workup and ALT elevations recovered when drug was stopped (positive dechallenge), the HAC assessed this case as probably related to tolerbrutinib.

Case #3. Participant enrolled in GEMINI 1 trial with monthly liver test monitoring

Participant with RMS with a history of migraines treated with paracetamol and mild transaminase elevations ($1.7 \times$ ULN) at baseline presented on Day 57 with nausea and ALT $31 \times$ ULN, AST $16.4 \times$ ULN, and TBILI within normal limits. Tolerbrutinib was discontinued and the participant was hospitalized on Day 60 with peak ALT of $98.7 \times$ ULN, AST $49.4 \times$ ULN, and TBILI $13.7 \times$ ULN. The participant was discharged on Day 82 and liver tests returned to baseline by Day 112. Confounding factors include mildly elevated transaminases at baseline, elevated iron panel parameters, and alcohol use. In addition, the pattern of elevation was concerning for viral illness but Hepatitis E testing was not performed. Due to these confounding factors, this event was assessed as possibly related to tolerbrutinib by the HAC.

Case #4. Participant enrolled in PERSEUS trial with monthly liver test monitoring

Participant with PPMS with previous liver dysfunction secondary to proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), and possibly alcohol use presented on Day 57 with ALT $2.6 \times$ ULN, AST $2.7 \times$ ULN, and TBILI within normal limits. The participant had a COVID-19 mRNA vaccine booster on Day 63. On Day

85 (Month 3 visit), the participant had nausea, vomiting, and elevated transaminases, and tolerbrutinib was discontinued the following day. By Day 92, peak ALT was reached: ALT $25.7 \times$ ULN, AST $23.8 \times$ ULN (peak Day 99 at $25.4 \times$ ULN), ALP $2.7 \times$ ULN, and TBILI $1.27 \times$ ULN, which later peaked on Day 106 at $2.7 \times$ ULN. The participant was hospitalized for further workup starting on Day 99 and was discharged on Day 113. Transaminases, ALP, and TBILI normalized by Day 155. Multiple comorbidities and confounders include history of prior liver dysfunction secondary to PPIs/NSAIDs, COVID-19 mRNA vaccine booster, ursodiol use, and presenting with a mixed injury followed by a subsequent idiosyncratic hepatocellular pattern. This event was assessed as possibly related to tolerbrutinib by the HAC. One HAC member concluded that this case did not fulfill Hy's Law criteria, citing atypical features including late onset of bilirubin elevation, presence of pruritus and initial ALP elevation suggesting cholestasis, and temporal evolution of the R value from mixed to hepatocellular injury. These features raised the possibility of alternative etiologies for the bilirubin elevation beyond classic drug-induced hepatocellular injury with jaundice.

Case #5. Participant enrolled in HERCULES trial with biweekly liver test monitoring

Participant with SPMS and a history of obesity and central serous chorioretinopathy, and a family history of liver disease of unknown etiology in maternal great grand aunt (died in her 30s of liver disease) and great grandmother. The participant presented on Day 44 with headache, constipation (started 4 days prior), nausea (worsening for 3 days), and concomitant vomiting, jaundice, and right upper quadrant tenderness, and ALT $50.4 \times$ ULN, AST $23.8 \times$ ULN, ALP $1.9 \times$ ULN, and

TBILI $6.3 \times \text{ULN}$. Tolebrutinib was discontinued on Day 43. International normalized ratio (INR) was normal on presentation but peaked at 3.7 on Day 71. Peak ALT of $65.0 \times \text{ULN}$ occurred on Day 51, peak AST of $49.5 \times \text{ULN}$ on Day 98, and peak TBILI of $31.4 \times \text{ULN}$ on Day 66. The participant was hospitalized on Day 52 and had a core liver biopsy on Day 56 revealing acute hepatitis with moderate portal and lobular inflammation, lymphocytic infiltrate largely with a CD8+ phenotype, without evidence of steatosis or fibrosis. The participant was transferred to another hospital on Day 66 and had a negative workup for other causes. Corticosteroid treatment was prescribed from Day 70 to Day 96 with improvement noted in INR values; the participant developed renal failure secondary to hepatic failure on Day 95. The participant underwent a liver transplant on Day 97 and experienced numerous post-surgical complications thereafter, including fungal infections (aspergillosis and *Pneumocystis jirovecii*, the latter being a labeled Warning and Precaution for BTK inhibitors), and died on Day 153. Genetic workup revealed the presence of the human leukocyte antigen *HLA-B*07:02* allele, which is of uncertain significance. This event was assessed as probably related to tolebrutinib by the HAC.

Case #6. Participant enrolled in LTS17043 with weekly liver test monitoring

Participant with RMS and obesity completed GEMINI 1 trial in the teriflunomide treatment arm and opted into Study LTS17043 (NCT06372145), initiating open-label tolebrutinib. The participant presented with an asymptomatic, isolated gamma-glutamyl transferase (GGT) elevation starting on Day 14. On Days 27 and 28, the participant was treated with “Tong ren tang fish maw pills” by a local pharmacist to treat the GGT elevation. On Day 29, liver tests were abnormal (ALT $29 \times \text{ULN}$, AST $18.9 \times \text{ULN}$, GGT $10.4 \times \text{ULN}$, and normal TBILI) and tolebrutinib was discontinued. ALT and AST peaked on Day 32 at $60.3 \times \text{ULN}$ and $34.8 \times \text{ULN}$, respectively, with TBILI peaking on Day 34 at $3.3 \times \text{ULN}$. The participant was hospitalized from Days 32 to 42 and complained of mild fatigue on Days 37 to 38. The liver tests trended downward from Day 42, and all values returned to normal by Day 76. Initially, the HAC assessed this case as probably related to tolebrutinib. Tong ren tang fish maw pills are an unregulated herbal and dietary supplement used in traditional Chinese medicine containing a poorly specified admixture of ingredients, including diosbulbin B and coumarin, both of which have been implicated as hepatotoxic substances in isolation. Laboratory testing in a human liver spheroid organoid assay system showed overall cytotoxicity for the fish maw pill in solution which was higher than the individual cytotoxicity of the two ingredients of the pills, diosbulbin B and coumarin. Following review of the cytotoxicity data, the HAC downgraded their assessment to possibly related to tolebrutinib due to the significant confounding factor of fish maw pills.

2.2. Protocol amendments for DILI management

Following the initial detection of liver enzyme elevations as a potential risk with tolebrutinib, study protocols were amended to incorporate more stringent inclusion and exclusion criteria for participants with baseline liver enzyme elevations or a history of hepatobiliary disorders including history of DILI. Treatment discontinuation criteria were also updated in accordance with the liver test monitoring protocols. A comprehensive summary of these protocol amendments is presented in Table 2.

These amendments were based on a detailed review of individual cases with ALT elevations $>8 \times \text{ULN}$ and the cases that met Hy’s law criteria. After implementing these amendments and enhanced liver test monitoring protocols to minimize the risk of DILI, the review of the data suggested that stringent enrollment and monitoring may mitigate the risk of Hy’s Law events, as some of the historical cases would have been excluded from enrollment or detected earlier to trigger treatment discontinuation as described in Section 2.3 below.

Table 2
Summary of protocol amendments following DILI risk identification.

Parameter	Initial protocol	Description of updates
Monitoring frequency	Monthly	May 2022: - Increased to biweekly from week 4 (every 2 weeks) September 2022: - Increased to weekly from week 4–12, with additional monitoring at week 2 November 2023: - Week 3 monitoring added, completing weekly monitoring from weeks 2 through 12
Inclusion/exclusion		
Baseline ALT, AST, ALP, TBILI	Any laboratory value outside normal limits deemed clinically significant by investigator	May 2022: Exclude if ALT or AST $>1.5 \times \text{ULN}$ OR ALP $>2 \times \text{ULN}$ OR TBILI $>1.5 \times \text{ULN}$ at screening (unless due to non-liver-related disorder)
Liver disease history	No specific exclusion	May 2022: Exclude acute liver disease, cirrhosis, chronic liver disease (unless stable for >6 months)
Alcohol use	Exclude history of alcohol or drug abuse within 1 year prior to screening	May 2022: - Exclude active alcohol use disorder or a history of alcohol or drug abuse within 1 year prior to screening - Exclude daily alcohol consumption (>2 drinks per day for men and >1 drink per day for women)
Iron panel	Not required	May 2022: Screening iron panel added to exclude participants with potential iron overload
ALT increase algorithm	Recommended treatment interruption at: - ALT $>3 \times \text{ULN}$ + TBILI $>2 \times \text{ULN}$, OR - ALT $>8 \times \text{ULN}$ if baseline ALT $>2 \times \text{ULN}$, OR - ALT $>5 \times \text{ULN}$ if baseline ALT $<2 \times \text{ULN}$ Consideration of alternative etiologies	May 2022: - Interruption at ALT $>5 \times \text{ULN}$ - Hepatology consult recommended - Rechallenge prohibited for Hy’s Law September 2022: - Required algorithm including DILI kit for all cases $>5 \times \text{ULN}$ - Mandatory hepatology consult for ALT $>8 \times \text{ULN}$ November 2023: - Rechallenge prohibited for Hy’s Law, ALT $>8 \times \text{ULN}$ and $>5 \times \text{ULN}$ (2 weeks) without alternative etiology - Guidance on interruption due to missed liver tests

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TBILI, total bilirubin; ULN, upper limit of normal.

2.3. Impact of weekly liver test monitoring on detection and recovery

Enhanced liver test monitoring was implemented stepwise, with monthly monitoring in the original study protocols, followed by biweekly and then weekly from week 2 through week 12 as implemented in the September 2022 amendment. In the 920 participants who underwent the enhanced liver test monitoring protocol, initial analyses demonstrated that a greater number of ALT $>3 \times$ ULN events were detected (4%) in the first 12 weeks compared to those exposed under the previous monitoring schedule (2.8%).

In cases where events with higher ALT elevations (ALT $>8 \times$ ULN) were designated as probably or possibly related to tolebrutinib by the HAC, a majority of events were detected between weeks 4 and 8 with a median treatment exposure of 6 weeks. Mean time to onset was 40 days with weekly monitoring ($n = 14$) compared to 60 days for participants enrolled prior to weekly monitoring ($n = 21$). Time to recovery (time from drug interruption to ALT $<1.5 \times$ ULN) was shorter with weekly monitoring (44 days vs 57 days) (Table 3).

These data support the effectiveness of the enhanced weekly liver test monitoring protocol in detecting ALT elevations early. The observed earlier recovery times provide evidence that this monitoring approach is an appropriate strategy for optimal risk mitigation of liver injury. As noted in Table 1, five Hy's Law cases out of 2006 exposed participants were observed prior to the implementation of enhanced liver test monitoring, compared with one confounded Hy's Law case among 920 participants after implementation of weekly monitoring.

3. Mechanistic studies to explore the etiology and biomarkers of DILI

3.1. Risk factor analyses

Following identification of the risk of liver injury, a comprehensive risk factor analysis was conducted using unblinded participant data from GEMINI 1, GEMINI 2, HERCULES, PERSEUS, and LTS17043. The following potential risk factors were considered after discussion with the HAC: body mass index (BMI), hepatobiliary disease, thyroid disease, alcohol use, concomitant medications (e.g., oral contraceptive, recent NSAIDs/acetaminophen use), and recent SARS-CoV-2 infection. Table 4 shows the frequency of risk factors in the 35 participants who had ALT $>8 \times$ ULN events assessed as probably or possibly related to tolebrutinib compared to 2803 tolebrutinib-treated participants who did not report ALT $>3 \times$ ULN events during study participation. The frequencies of risk factors were similar to or less than those observed in participants who had liver events compared to those on tolebrutinib without ALT elevations during study participation, with the exception of hepatobiliary disease and thyroid disease. Although the frequency of thyroid disease was higher in participants with liver injury (17.1% vs 8.6%), all six participants with ALT $>8 \times$ ULN events were managed with levothyroxine for at least 1 year prior to the event. Therefore, the contribution of levothyroxine to the observed hepatotoxicity is unlikely.

This analysis has limitations as the relatively low incidence of severe

Table 3

Impact of weekly liver test monitoring on time to onset and time to recovery of ALT elevations $>8 \times$ ULN without alternative etiology.

Parameter	Pre-enhanced monitoring ($n = 2006$)	Enhanced weekly monitoring ($n = 920$) ^a
Time to onset, mean (days)	60	40
Time to recovery, mean (days)	57	44

ALT, alanine aminotransferase; ULN, upper limit of normal.

^a 952 participants enrolled in weekly monitoring and 920 of those completed at least the first 12 weeks.

Table 4

Assessment of potential risk factors for drug-induced liver injury.

Parameters	ALT $>3 \times$ ULN + TBILI $>2 \times$ ULN OR ALT $>8 \times$ ULN ($n = 35$) ^a (Probably or possibly related cases on tolebrutinib)		No ALT $>3 \times$ ULN ($n = 2803$)	
	Mean	SD	Mean	SD
Age	40.7	10.5	42.9	10
Potential Risk Factor	Number (n)	Frequency (% out of 35)	Number (n)	Frequency (% out of 2803)
Gender (% female)	26	74.2	1692	60.4
BMI (>30)	6	17.1	489	17.5
Hepatobiliary disease	4	11.4	82	2.9
Thyroid disease	6	17.1	249	8.9
Alcohol use ^b	15	42.9	1438	51.3
Oral contraceptive use	4 ^c	11.4	262	9.3
NSAID use	5 ^d	14.3	962	34.3
Acetaminophen/Paracetamol use	0 ^d	0	1011	36.1
COVID-19 infection	4	11.4	580	20.7

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TBILI, total bilirubin; ULN, upper limit of normal.

^a Probably or possibly related cases assessed by Hepatology Assessment Committee.

^b Participants reported at least occasional alcohol use.

^c Concurrent use at time of ALT elevation.

^d Recent use defined as concurrent or within 1 week prior to ALT elevation.

liver injury limits the statistical power to identify specific risk factors or predictive biomarkers, even in those factors with numerical discrepancies. Additionally, the idiosyncratic nature of the liver injury makes it challenging to predict which patients may be at higher risk.

In addition to the above approach, clinical machine learning models were developed and validated to predict risk factors using study data from ALT elevation cases as well as routinely collected healthcare data. However, no actionable risk factors emerged from this analysis either, likely due to the same limitations. This additional risk factor analysis included a full assessment of potentially hepatotoxic medications as categorized by the FDA Drug-Induced Liver Injury Severity and Toxicity Dataset (Thakkar et al., 2020).

3.2. Genetic analysis

A case-control pharmacogenetic assessment was conducted to evaluate genetic variation in HLA genes as a potential risk factor for DILI in tolebrutinib-exposed participants. In September 2022, 18 study participants with events of ALT $>8 \times$ ULN consented to pharmacogenetic analysis. All cases had received tolebrutinib and were deemed probably or possibly related to tolebrutinib based on independent HAC assessments. Controls without treatment-emergent ALT elevations above the normal range were matched to cases based on study, age, sex, BMI, ethnicity, treatment assignment, and treatment duration exceeding 60 days. Genetic variation in HLA genes for DILI cases and controls was characterized by targeted sequencing of 11 Class I and II HLA genes using next-generation sequencing and by genotyping for variants that have been previously associated with adverse drug reactions, including DILI, using a microarray platform.

The primary analysis of both the sequencing and genotyping data focused on 32 HLA variants that have been previously reported to be associated with DILI. Targeted sequencing identified 17 of these 32 HLA variants in 18 cases and 109 controls. Given the limited sample size, the preliminary data did not support definitive conclusions.

3.3. Mechanistic investigations using liver spheroids

Mechanistic studies using liver spheroids provided insights into the potential etiology of tolebrutinib-associated DILI. Following identification of the risk of liver injury in clinical studies, in vitro studies were performed to assess cytotoxicity of tolebrutinib and other BTK inhibitor targeting compounds using liver spheroids, an in vitro organoid system that displays many functional properties of hepatocytes in vivo.

Whole genome transcript profiling in human, rat, and dog liver spheroids exposed to tolebrutinib and its major active metabolite (M2) showed similar findings across all three species, with no evidence of direct hepatocellular toxicity. The in vitro cytotoxicity (IC₅₀) of tolebrutinib and M2 in human-derived liver spheroids was 32.6 μM, approximately 1000-fold higher than the maximum plasma concentration (C_{max}) exposure achieved clinically. Comparable values for direct cytotoxicity were observed across rat, dog, and human-derived organoid models, suggesting low potential for direct cytotoxicity.

Furthermore, exposure-response analysis showed that the cumulative probability of hepatic enzyme elevations (ALT or AST >3 ×, 5 ×, or 8 × ULN) over time did not demonstrate any clear trend between liver injury and exposure across placebo and quartiles of AUC for tolebrutinib plus M2 (Table 5).

4. Risk mitigation strategies

Liver injury has emerged as a risk associated with other BTK inhibitors in both oncology and MS indications, suggesting a potential class effect (Tafesh et al., 2019; Montalban et al., 2019; Oh et al., 2025; Fox et al., 2025; Bar-Or et al., 2026). In response to the accumulating safety data from tolebrutinib Phase 3 trials and other BTK inhibitors, comprehensive risk mitigation strategies were implemented through protocol amendments. Key modifications included: (1) updated benefit-risk assessments; (2) more stringent enrollment criteria to exclude individuals with elevated baseline liver enzyme laboratory values; (3) enhanced liver test monitoring protocol frequency to weekly testing for the first 12 weeks; (4) modified liver injury monitoring algorithms; and (5) revised treatment interruption and rechallenge criteria. These measures were designed to identify at-risk individuals early, discontinue treatment when appropriate, and minimize the risk of severe liver injury. Since full implementation of these enhanced liver test monitoring protocols was initiated, only one Hy's Law case (with significant confounding factors) was identified among 920 newly exposed trial participants (0.11%).

Table 5
Exposure-response analysis for ALT or AST elevations >8 × ULN by tolebrutinib AUC quartiles in HERCULES and GEMINI 1 trials.

Exposure (AUC) quartile (ng·h/mL, min-max)	No. of participants	No. of participants with event [n (%)]	Hazard ratio vs placebo (95% CI)
Placebo	375	1 (0.3%)	
Tolebrutinib Q1 (1.1–16.9)	278	6 (2.2%)	7.2 (0.9–59.7)
Q2 (17.0–27.2)	278	4 (1.4%)	5.0 (0.6–44.3)
Q3 (27.3–39.6)	279	3 (1.1%)	3.6 (0.4–35.0)
Q4 (39.7–129.9)	279	0 (0.0%)	Not estimable
Teriflunomide	488	5 (1.0%)	3.4 (0.4–29.2)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; ULN, upper limit of normal.

5. Summary and conclusions

Liver injury was identified as an important risk with tolebrutinib exposure. While no significant liver injury findings were identified in preclinical studies or during early clinical development, including Phase 2 trials, liver-related adverse events emerged during the Phase 3 program, where five of 2006 participants met Hy's Law criteria prior to the implementation of enhanced liver test monitoring protocols. One participant required a liver transplant and had a fatal outcome due to postoperative complications; notably, this case occurred prior to the implementation of enhanced liver test monitoring during the first 12 weeks of tolebrutinib treatment initiation. All other participants with confirmed Hy's Law fully recovered following tolebrutinib discontinuation. One additional participant (1/920; 0.11%) met Hy's Law criteria in the LTS17043 study under the enhanced liver test monitoring protocols. However, this case was confounded by obesity, isolated GGT elevation, and ingestion of an herbal supplement subsequently shown to be hepatotoxic in liver spheroid assays. This participant fully recovered upon discontinuation.

The mechanistic investigations using liver spheroids and exposure-response analyses support the hypothesis that tolebrutinib-associated liver injury results from an idiosyncratic mechanism, possibly immune-mediated, rather than direct dose-dependent hepatotoxicity, consistent with findings observed across MS and the lack of a clear exposure-response relationship in clinical studies. Temporal analyses indicated that the highest risk of liver injury was observed within the first 90 days following tolebrutinib initiation. With the exception of Hy's Law cases, events were generally mild and reversible upon discontinuation. However, strict adherence to liver test monitoring requirements, and prompt management of liver enzyme elevations, are important to mitigate DILI risk.

Although tolebrutinib carries an identified risk of liver injury, it showed significant slowing of disability progression in people with nrSPMS, a population with high unmet need, which led to the European Medicines Agency (EMA) approval on June 19, 2026, for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (EMA, 2026).

Enhanced liver test monitoring protocols, including weekly liver test monitoring for the first 12 weeks, have proved to be effective in enabling early detection and faster recovery, indicating improved risk mitigation.

Appropriate liver safety monitoring improves the benefit-risk profile of continued development of tolebrutinib for patients with SPMS without relapses.

Ethics statement

The clinical trials described in this manuscript (GEMINI 1 [NCT04410978], GEMINI 2 [NCT04410991], HERCULES [NCT04411641], PERSEUS [NCT04458051], and LTS17043 [NCT06372145]) were conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Study protocols were approved by the institutional review boards or independent ethics committees at each participating site. All participants provided written informed consent prior to enrollment.

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The clinical trials reported in this manuscript (GEMINI 1 [NCT04410978], GEMINI 2 [NCT04410991], HERCULES [NCT04411641], PERSEUS [NCT04458051], and LTS17043 [NCT06372145]) were funded and sponsored by Sanofi.

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analysis, Methodology, Writing – original draft, Writing – review & editing. **Timothy J. Turner:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Erik Wallstroem:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Suhad Patel:** Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Stephen C. Pappas:** Formal analysis, Writing – review & editing. **James H. Lewis:** Formal analysis, Writing – review & editing. **Raúl J. Andrade:** Formal analysis, Writing – review & editing. **Sana Syed:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

CRM, TJT, EW, SP, and SS are employees of Sanofi and may hold shares and/or stock options in the company. SCP is a member of the Hepatology Assessment Committee (HAC) in the tolebrutinib trial program. He has received consulting fees and compensation for Safety Review Board participation from Sanofi, Boehringer Ingelheim, Mallinckrodt Pharmaceuticals, Orphan Therapeutics LLC, Arrowhead Pharmaceuticals, Zealand Pharma. JHL is a member of the HAC in the tolebrutinib trial program, and has received compensation from Sanofi. RJA is a member of the HAC in the tolebrutinib trial program, and has received compensation as a consultant/advisor from Abbott, Aptierion Biotech, Bayer, BMS, Boehringer Ingelheim, ENYO, GSK, Inventiva, IN SILICO Medicine, iQure, Ipsen, Johnson & Johnson, Kainos Medicine, Novo Nordisk, Roche, Ryvu Therapeutics, and Sanofi.

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Data availability

<https://www.vivli.org> (Qualified researchers may request access to individual-level data and related documents, including clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Individual-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at:.)

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