

## **ZYNLONTA® (loncastuximab tesirine-lpyl)- Incidence of Hepatic Enzyme Abnormalities**

### **Summary**

- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study that evaluated the safety and tolerability of loncastuximab tesirine-lpyl (Lonca) monotherapy in 183 adult patients with relapsed or refractory B-cell non-Hodgkin lymphoma (R/R B-NHL). The study was conducted in two parts: dose escalation (Part 1) followed by dose expansion (Part 2).<sup>4,6</sup>
  - Among the total patient population (Part 1 + Part 2), all-grade treatment-emergent adverse events (TEAEs) included gamma-glutamyltransferase (GGT) increase (57 patients, 31.1%), blood alkaline phosphatase (ALP) increase (37 patients, 20.2%), aspartate aminotransferase (AST) increase (34 patients, 18.6%), and alanine aminotransferase (ALT) increase (32 patients, 17.5%).
  - Across all Lonca doses combined, Grade  $\geq 3$  GGT increase occurred more frequently than Grade  $\geq 3$  ALP, AST, or ALT increases. GGT increase (19 patients, 10.4%) was the most common hepatic TEAE leading to dose delay.
  - ALT and AST increase (2 of 183 patients, 1.1% each) and blood ALP increase (6 of 183 patients, 3.3%) were TEAEs leading to dose delay.
  - ALT, AST, blood ALP, and GGT increase each led to dose reduction in 1 patient (0.5%).
  - GGT increase led to treatment discontinuation in 5 patients (2.9%).
- LOTIS-2 was a pivotal Phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA monotherapy in 145 adult patients with R/R diffuse large B-cell lymphoma (DLBCL) following  $\geq 2$  prior lines of systemic therapy.<sup>5,7</sup>
  - Long-term safety analyses demonstrated GGT increase in approximately 42% of patients (any grade), making it one of the most frequently reported laboratory abnormalities.
  - Grade  $\geq 3$  GGT elevation occurred in approximately 17% of patients and was generally not associated with concurrent clinically meaningful ALT or AST elevations or evidence of acute liver failure.
- As part of ADC Therapeutics' ongoing pharmacovigilance activities, cases of hepatotoxicity, including drug-induced liver injury (DILI), have been identified in the ZYNLONTA safety database, including a fatal case. As of January 22, 2026, the ZYNLONTA United States Prescribing Information (USPI) includes a Warning and Precaution for Hepatotoxicity, including DILI.
  - Liver function tests should be monitored at baseline and throughout treatment. In the event of suspected DILI or Grade  $\geq 3$  ALT or AST elevation, ZYNLONTA should be withheld until toxicity resolves to Grade 1 or lower; upon confirmation of DILI, ZYNLONTA should be permanently discontinued. ZYNLONTA should be avoided in patients with severe hepatic impairment.<sup>8</sup>
- Clinical study protocol guidance reflects knowledge available at the time of LOTIS-2 initiation and differs from current USPI recommendations, which incorporate additional safety data from LOTIS-2 and postmarketing pharmacovigilance.
- Refer to the [Relevant Prescribing Information](#) section for further information regarding hepatic enzyme abnormalities and risk management in patients receiving ZYNLONTA.

## Background

- ZYNLONTA is a CD19-directed antibody drug conjugate composed of a humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody conjugated via a protease-cleavable valine alanine linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent. The linker payload complex is designated SG3249 (tesirine).<sup>4,5</sup>
- Gamma-glutamyltransferase (GGT) is an enzyme involved in glutathione and cysteine metabolism and is expressed in multiple tissues, including the liver, kidney, pancreas, intestine, and prostate.<sup>1,2,3</sup>
  - GGT is a component of routine hepatic chemistry testing and may reflect biliary tract involvement; levels may also be influenced by enzyme-inducing medications, alcohol use, and comorbid conditions.<sup>1,2,3</sup>
  - Typical adult reference ranges for GGT are approximately 8–78 units per liter (U/L), though ranges may vary by laboratory.<sup>2</sup>
- Hepatic enzyme abnormalities observed with ZYNLONTA are considered likely related to the PBD warhead, based on class effects observed with other PBD-containing antibody–drug conjugates and the pattern of laboratory abnormalities reported in LOTIS-1 and LOTIS-2.<sup>1,2,3</sup>

## Clinical Data

### LOTIS-1

- LOTIS-1 evaluated ZYNLONTA monotherapy in 183 adult patients with R/R B-NHL.<sup>4</sup>
  - In Part 1, 88 patients received Lonca every 3 weeks (Q3W) at doses ranging from 15–200 µg/kg.
  - In Part 2, 26 patients received Lonca 120 µg/kg Q3W and 69 patients received Lonca 150 µg/kg Q3W; some patients in the 150 µg/kg cohort reduced the dose to 75 µg/kg Q3W after three cycles.

### Hepatic Enzyme Abnormalities<sup>4,6</sup>

- Among all treated patients, all-grade GGT, ALP, AST, and ALT increases occurred at rates of 31.1%, 20.2%, 18.6%, and 17.5%, respectively. Incidences varied by dose level. Incidences of hepatic enzyme abnormalities at varying Lonca doses are shown in [Table 1](#).
- Liver enzyme abnormalities were more frequent at higher Lonca dose levels, particularly at 200 µg/kg.
- GGT levels appeared to increase over time, especially at higher dose levels.
- ALT, AST, and bilirubin generally showed mild, transient increases from baseline with recovery between cycles and no evidence of cumulative worsening across cycles.
- ALP demonstrated a modest increase early in treatment, with less pronounced changes in later cycles.

**Table 1.** Incidence of All-grade Hepatic Test Abnormalities in LOTIS-1. Adapted from Hamadani M et al.2021.<sup>4</sup>

TEAE, n (%)	Dose (µg/kg)				Total (N=183)
	≤90	120	150	200	
	Part 1 (n=17)	Part 1+2 (n=42)	Part 1+2 (n=88)	Part 1 (n=36)	
GGT increase	5 (29.4)	13 (31.0)	22 (25.0)	17 (47.2)	57 (31.1)
Blood ALP increase	4 (23.5)	6 (14.3)	18 (20.5)	9 (25.0)	37 (20.2)
AST increase	3 (17.6)	5 (11.9)	15 (17.0)	11 (30.6)	34 (18.6)
ALT increase	3 (17.6)	6 (14.3)	14 (15.9)	9 (25.0)	32 (17.5)

Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase;; GGT, gamma-glutamyltransferase

- For all doses combined, Grade ≥ 3 GGT increase was much more common than any increase in Grade ≥3 ALP, AST, or ALT.<sup>7,9</sup> Please see **Table 2** below.

**Table 2.** Incidence of Grade ≥3 Hepatic Test Abnormalities. Adapted from Hamadani M. et al.2021 and LOTIS-1 Data on File.<sup>6</sup>

TEAE, n (%)	Dose (µg/kg)				Total (N=183)
	≤90	120	150	200	
Preferred Term	Part 1 (n=17)	Part 1+2 (n=42)	Part 1+2 (n=88)	Part 1 (n=36)	
Any Grade ≥3 TEAE	9 (52.9)	32 (76.2)	69 (78.4)	31 (86.1)	141 (77.0)
GGT increase	4 (23.5)	9 (21.4)	15 (17.0)	11 (30.6)	39 (21.3)
Blood ALP increase	4 (23.5)	3 (7.1)	3 (3.4)	2 (5.6)	12 (6.6)
AST increase	0 (0)	1 (2.4)	1 (1.1)	3 (8.3)	5 (2.7)
ALT increase	1 (5.9)	2 (4.8)	3 (3.4)	2 (5.6)	8 (4.4)

Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase

#### Dose Delays, Dose Reductions, and Treatment Discontinuation<sup>4,6</sup>

- GGT increase (19 patients, 10.4%) was the most common hepatic TEAE leading to dose delay.
- ALT, AST (2 patients each, 1.1%), and blood ALP increase (6 patients, 3.3%) also led to dose delays.
- ALT, AST, blood ALP, and GGT increase each led to dose reduction in 1 patient (0.5%).
- GGT increase resulted in treatment discontinuation in 5 patients (2.9%).

#### LOTIS-2

- LOTIS-2 evaluated ZYNLONTA monotherapy in 145 adult patients with R/R DLBCL after ≥2 prior lines of therapy.<sup>5</sup>
  - ZYNLONTA was administered as a 30-minute intravenous infusion on Day 1 of each 21-day cycle at 150 µg/kg Q3W for the first two cycles, followed by 75 µg/kg Q3W for subsequent cycles, for up to one year or until discontinuation criteria were met.

### Hepatic Enzyme Abnormalities- Final Analysis of LOTIS-2 Study

- Final analysis of LOTIS-2 revealed the following:<sup>5</sup>
  - Grade ≥3 GGT increase was reported in 25 patients (17.2%).
  - GGT increase led to dose delay in 26 patients (17.9%).
  - GGT increase led to treatment discontinuation in 17 patients (11.7%).

### Management of Liver Enzyme Abnormalities

- Dose delays and reductions were used to manage hepatic enzyme elevations in the LOTIS-2 trial.<sup>7</sup>
- Per the LOTIS-2 protocol, patients with recurrent Grade ≥2 GGT elevation after two dose reductions or dose delays exceeding five weeks were discontinued from treatment. This protocol driven approach does not necessarily reflect current clinical practice, as isolated GGT elevation without concomitant ALT or AST abnormalities may not warrant treatment discontinuation in responding patients.<sup>5</sup>
- Consistent with current prescribing information, liver function tests should be monitored at baseline and throughout treatment. In cases of suspected DILI or Grade ≥3 ALT or AST elevation, ZYNLONTA should be withheld until recovery to Grade 1 or lower; upon confirmation of DILI, ZYNLONTA should be permanently discontinued. ZYNLONTA should be avoided in patients with severe hepatic impairment.<sup>8</sup>

### Literature Search

- A PubMed biomedical literature search conducted on January 25, 2026, identified no additional peer reviewed publications providing new clinical data on the incidence of hepatic enzyme abnormalities associated with ZYNLONTA.

### Relevant Prescribing Information

#### Section 2: Dosage and Administration<sup>8</sup>

#### 2.3 Delays and Modifications

**Table 3: Delays and Modifications.** Adapted from Prescribing Information<sup>8</sup>

Adverse Reactions	Severity <sup>a</sup>	Dosage Modification
<b>Nonhematologic Adverse Reactions</b>		
Hepatotoxicity [see Warnings and Precautions (5.4)]	Grade 3a or higher increase in AST or ALT or suspected DILI	Withhold ZYNLONTA until toxicity resolves to Grade 1 or less, discontinue for confirmed DILI
Other Adverse Reactions [see Warnings and Precautions (5.3), (5.5), Adverse Reactions (6.1)]	Grade 3a or higher	Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less

<sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

- If dosing is delayed by more than 3 weeks due to toxicity related to ZYNLONTA, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation.
- Note: If toxicity requires dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the dose of 0.075 mg/kg for Cycle 3.

#### Section 5.4: Hepatotoxicity, Including Drug-Induced Liver Injury

- Cholestatic and hepatocellular liver injury, including severe, life-threatening, and fatal cases of drug-induced liver injury (DILI), have occurred in patients treated with ZYNLONTA.
- Monitor liver function tests at baseline and throughout treatment with ZYNLONTA. In the event of suspected DILI or Grade  $\geq 3$  increase in ALT or AST, withhold ZYNLONTA until toxicity resolves to Grade 1 or lower. Upon confirmation of DILI, discontinue ZYNLONTA. [see Dosage and Administration (2.3)].
- ZYNLONTA should be avoided in patients with severe hepatic impairment [see Clinical Pharmacology (8.6, 12.3)].

#### Section 6.1: Clinical Trials Experience<sup>8</sup>

##### Relapsed or Refractory Diffuse Large B-cell Lymphoma

**Table 4: Hepatic Enzyme Abnormalities ( $\geq 10\%$ ) That Worsened from Baseline in Patients with Relapsed or Refractory DLBCL Who Received ZYNLONTA in LOTIS-2.** Adapted from Prescribing Information.<sup>8</sup>

Chemistry	ZYNLONTA <sup>a</sup>	
	All Grades (%)	Grade 3 or 4 (5)
GGT increased	57	21
AST increased	41	<1 <sup>b</sup>
ALT increased	34	3

<sup>a</sup> The denominator used to calculate the rate varied from 143 to 145 based on the number of patients with a baseline value and at least one post-treatment value

<sup>b</sup> No Grade 4 adverse reactions occurred

##### Other Clinical Trials Experience

- The following adverse reactions have been reported following administration of ZYNLONTA:
  - Hepatotoxicity, including drug-induced liver injury (DILI).

#### Section 8: Use in Specific Populations<sup>6</sup>

##### Section 8.6: Hepatic Impairment<sup>6</sup>

- No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin  $\leq$  upper limit of normal [ULN] and aspartate aminotransferase (AST)  $>$  ULN or total bilirubin  $> 1$  to  $1.5 \times$  ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions [see Dosage and Administration (2.3)].
- There is limited safety information available in patients with moderate hepatic impairment. ZYNLONTA should be avoided in patients with severe hepatic impairment [see Clinical Pharmacology (12.3)].

#### Section 12: Clinical Pharmacology<sup>8</sup>

##### 12.2 Pharmacodynamics

- Higher loncastuximab tesirine-lpyl exposure in Cycle 1 was associated with higher incidence of some Grade  $\geq 2$  adverse reactions, including skin and nail reactions, liver function test abnormalities and increased gamma-glutamyltransferase. Lower loncastuximab tesirine-lpyl exposure in Cycle 1 was associated with lower efficacy over the dose range of 0.015-0.2 mg/kg (0.1 to 1.33 times the maximum recommended dose).

### 12.3 Pharmacokinetics

#### Patients with Hepatic Impairment

- Mild hepatic impairment (total bilirubin  $\leq$  ULN and AST  $>$  ULN, or total bilirubin  $>1$  to  $1.5 \times$  ULN and any AST) may increase the exposure of unconjugated SG3199, however there was no clinically significant effect on loncastuximab tesirine-lpyl pharmacokinetics. There is insufficient data in patients with moderate (total bilirubin  $>1.5$  to  $\leq 3 \times$  ULN and any AST) hepatic impairment or severe (total bilirubin  $>3$  ULN and any AST) hepatic impairment.

## References

- <sup>1</sup>Neuman MG, Malnick S, Chertin L. Gamma glutamyl transferase - an underestimated marker for cardiovascular disease and the metabolic syndrome. *J Pharm Pharm Sci.* 2020;23(1):65-74. doi: 10.18433/jpps30923.
- <sup>2</sup>Lala V, Goyal A, Bansal P, Minter DA. Liver Function Tests. 2021 Aug 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29494096.
- <sup>3</sup>Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol.* 2017 Jan;112(1):18-35. doi: 10.1038/ajg.2016.517. Blood Tests: Normal Values. Merck Manual. <https://www.merckmanuals.com/professional/resources/normal-laboratory-values/blood-tests-normal-values#v8508814> . Last updated September 2018. Accessed January 25, 2026.
- <sup>4</sup>Hamadani M, Radford J, Carlo-Stella C, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. *Blood.* 2021 May 13;137(19):2634-2645. doi: 10.1182/blood.2020007512.
- <sup>5</sup>Caimi PF, Ai WZ, Alderuccio JP, et al. Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase 2 LOTIS-2 study. *Haematologica.* 2024; 109:1184-1193
- <sup>6</sup>Data on File, LOTIS-1 Clinical Study Report. ADC Therapeutics.
- <sup>7</sup>Data on File, LOTIS-2 Clinical Study Report. ADC Therapeutics.
- <sup>8</sup>ZYNLONTA® (loncastuximab tesirine-lpyl) for injection Prescribing Information, January 2026.

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**ADC Therapeutics encourages all health care professionals to report any adverse events and product quality complaints to medical information at 855-690-0340. Please consult the ZYNLONTA Prescribing Information.**