# ZYNLONTA® (loncastuximab tesirine-lpyl) - Incidence of Thrombocytopenia

## 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 (R/R) B-cell Non-Hodgkin Lymphoma (B-NHL).[1]
    - Among the safety analysis set of 183 patients (Part 1 + Part 2), all-grade levels of platelet count decrease were reported in 128 patients (71.1%).[1]
    - Platelet counts revealed a general trend of decrease and recovery; this pattern was most pronounced at 200 µg/kg, with limited partial platelet recovery reflective of accumulating toxicity at this dose.[1]
    - Among the safety analysis set of 183 patients, Grade ≥3 platelet count decrease was reported in 48 patients (26.7%).[1]
    - Grade 4 thrombocytopenia was reported in 1 patient receiving Lonca 120 µg/kg, while Grade 4 thrombocytopenia was reported in 2 patients receiving Lonca 200 µg/kg.[1]
    - Of the total patient population, thrombocytopenia led to dose delays in 4 patients (2.2%).[3]
    - Grade ≥3 hematology abnormalities were common, and thrombocytopenia was the second leading cause of treatment discontinuation in 5 patients (2.7%).[1]
- LOTIS-2 was a pivotal Phase 2, open-label, single-arm, multicenter study that evaluated the efficacy and safety of ZYNLONTA monotherapy in 145 adult patients with R/R diffuse large B-cell lymphoma (DLBCL) following ≥2 lines of prior systemic therapy.[2]
    - The long-term efficacy and safety of the LOTIS-2 study, data cut-off, September 15, 2022, revealed the following:
        - Grade ≥3 thrombocytopenia was common and occurred in 26 patients (17.9%).[7]
    - In the LOTIS-2 study, data cut-off April 06, 2020, the following was reported:[2]
        - Of the all-treated population of 145 patients, 48 patients (33.1%) experienced all-grade thrombocytopenia.[2]
        - Grade ≥3 thrombocytopenia was reported in 26 patients (18%).[2]
        - Dose delays were used to manage hematological events; thrombocytopenia (9%, 13 patients) was a common cause of dose delay.[2]
        - Thrombocytopenia led to dose reduction in 1 patient (<1%).[2]
        - Thrombocytopenia led to drug discontinuation in 2 patients (1.4%).[6]
- In LOTIS-2, when analyzing thrombocytopenia by age groups, there was a tendency towards a higher incidence of thrombocytopenia in the <65 years age group (28 of 65 patients; 43.1%), compared with the ≥65 years age group (20 of 80 patients; 25.0%) (data cut-off, August 06, 2020).[5]
- For patients who experience thrombocytopenia (platelet count less than 50,000/µL), withhold ZYNLONTA until platelet count returns to 50, 000/µL or higher.**Error! Bookmark not defined.**
- See the **Relevant Prescribing Information** section for additional information regarding thrombocytopenia in patients receiving ZYNLONTA.

## Background

- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study that evaluated the safety and tolerability of Lonca monotherapy in 183 adult patients with R/R B-NHL. The study was conducted in two parts, dose-escalation (Part 1), followed by dose-expansion (Part 2).[1]
    - In Part 1 (dose-escalation), 88 patients received treatment with Lonca at doses 15–200 µg/kg every 3 weeks (Q3W).
    - In Part 2 (dose-expansion), 26 patients received Lonca 120 µg/kg Q3W and 69 patients received Lonca 150 µg/kg Q3W, with some patients in the 150 µg/kg dose cohort reducing their dose to 75 µg/kg Q3W after 3 cycles. This dose reduction was based on an increase in cumulative toxicities observed at the 200 µg/kg dose and evidence of activity of Lonca at the 120 µg/kg and 150 µg/kg dose during Part 1.
    - Patients received a median of 2 Lonca doses (range 1–24) for a median treatment duration of 64 days (range 22–532).
- LOTIS-2 was a Phase 2, open-label, single-arm, multicenter study that evaluated the efficacy and safety of ZYNLONTA monotherapy in 145 adult patients with R/R DLBCL following ≥2 lines of prior systemic therapy.[2]
    - ZYNLONTA was administered as a 30-minute intravenous (IV) infusion on Day 1 of each 21-day cycle, at a dose of 150 µg/kg (0.15 mg/kg) every three weeks (Q3W) for the first 2 cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles for up to one year or until disease relapse or progression, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient, investigator, or sponsor decision.
    - Median treatment duration was 45.0 days (interquartile range [IQR] 22.0 to 113.0); this number reflects treatment discontinuation for patients with disease progression at Cycle 2 disease assessments.
    - The median number of treatment cycles was 3.0 (IQR: 2.0–5.0 and range: 1-15).

## Clinical Data

*LOTIS 1 (Phase 1)*

*Platelet Count Decrease*

- Among the safety analysis set of 183 patients (Part 1 + Part 2), all grade levels of platelet count decrease were reported in 128 patients (71.1%).[1]
- Platelet counts revealed a general trend of decrease and recovery; this pattern was most pronounced at 200 µg/kg, with limited partial platelet recovery reflective of accumulating toxicity at this dose.[1]
- Grade 3 or 4 platelet count decreases were most common during the first 2 cycles of Lonca; patients with prolonged events had treatment withdrawn.[1]
- See **Table 1** for additional information regarding all-grade platelet count decrease in patients receiving Lonca at varying doses in LOTIS-1.

**Table 1.** All-Grade Platelet Count Decrease in LOTIS-1 (Safety Analysis Set). Adapted from Hamadani, et al. *Blood*. 2020[1]

| TEAE, n (%) | Dose (µg/kg) | | | | |
|---|---|---|---|---|---|
| | ≤90 (n=17) | 120 (n=42) | 150 (n=88) | 200 (n=36) | Total (N=183) |
| Platelet count decreased[a] | 11 (64.7) | 28 (68.3) | 62 (71.3) | 22 (77.1) | 128 (71.1) |

[a]Platelet count decreased is based on laboratory abnormality reporting and are reported out of number of patients with postbaseline test values; data for 3 patients (1 each at 120, 150, and 200 µg/kg) were missing for platelet count decreased. Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion

- Among the safety analysis set of 183 patients, Grade ≥3 platelet count decrease was reported in 48 patients (26.7%).[1]
- See **Table 2** below for further information regarding Grade ≥3 platelet count decrease at various Lonca doses in LOTIS-1.

**Table 2.** Grade ≥3 Platelet Count Decrease in LOTIS-1 (Safety Analysis Set). Adapted from Hamadani, et al. *Blood*. 2020[1]

| TEAE, n (%) | Dose (µg/kg) | | | | |
|---|---|---|---|---|---|
| | ≤90 (n=17) | 120 (n=42) | 150 (n=88) | 200 (n=36) | Total (N=183) |
| Platelet count decreased[a] | 1 (5.9) | 7 (17.1) | 25 (28.7) | 15 (42.9) | 48 (26.7) |

[a]Platelet count decreased is based on laboratory abnormality reporting; data for 3 patients (1 each at 120, 150, and 200 µg/kg) were missing for platelet count decreased. Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion

*Thrombocytopenia and Dose-Limiting Toxicity (DLT)*

- A hematologic DLT was defined as Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with clinically significant bleeding, or Grade 3 thrombocytopenia requiring a platelet transfusion.[3]
- Of the 73 patients within the DLT set, Grade 4 thrombocytopenia was reported in 1 patient receiving Lonca 120 µg/kg, while Grade 4 thrombocytopenia was reported in 2 patients receiving Lonca 200 µg/kg.[1]

*Dose Delays, Dose Reductions, and Treatment Discontinuation*

- Of the total patient population, thrombocytopenia led to dose delays in 4 patients (2.2%).[3]
- Grade ≥3 hematology abnormalities were common, and thrombocytopenia was the second leading cause of treatment discontinuation in 5 patients (2.7%).[1]

*LOTIS-2 (Phase 2)*

*Follow-up Analysis and Long-term efficacy and safety of LOTIS-2 Study (Data Cut-Off, March 01, 2021, September 15, 2022)*

- Grade ≥3 thrombocytopenia was common and occurred in 26 patients (17.9%).[4]
- In the long-term efficacy and safety that included analyses of subsets of patients with durable complete response (CR), Grade ≥3 thrombocytopenia in the all-treated population remained the same, Grade ≥3 thrombocytopenia in patients with CR occurred in 13 patients (36.1%) out of 36 patients.[7]

*Caimi PF, et al. Lancet Oncol. 2021 and LOTIS-2 Data on File (Data Cut-Off, April 6, 2020)*

- Of the all-treated population of 145 patients, 48 patients (33.1%) experienced all-grade thrombocytopenia.[2]
- Grade ≥3 thrombocytopenia was reported in 26 patients (18%) as shown in **Table 3** below.[2]
- When analyzing thrombocytopenia by age groups, there was a tendency towards a higher incidence of thrombocytopenia in the <65 years age group (28 of 65 patients; 43.1%), compared with the ≥65 years age group (20 of 80 patients; 25.0%).[5]

**Table 3.** Incidence Thrombocytopenia, LOTIS-2 (Data Cut-Off, April 6, 2021). Adapted from Caimi PF, et al. *Lancet Oncol*. 2020.[2]

| TEAE, n (%) | All-Treated Population (N=145) | | | |
|---|---|---|---|---|
| | **Grade 1–2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Thrombocytopenia | 22 (15%) | 18 (12%) | 8 (6%) | 0 |

Data are n (%). Treatment-emergent adverse events are shown if they occurred in 10% of patients or more at Grade 1–2, or in any patient at Grade 3, 4, or 5.

*Dose Delays, Dose Reductions, and Treatment Discontinuations*

- Dose delays were used to manage hematological events; thrombocytopenia (9%, 13 patients) was a common cause of dose delay.[2]
- Thrombocytopenia led to dose reduction in 1 patient (1%).[2]
- Thrombocytopenia led to drug discontinuation in 2 patients (1.4%).[6]

*Management of Thrombocytopenia*

- Dose delays and reductions were used to manage thrombocytopenia.[1,2]
- The LOTIS-2 study protocol permitted two dose reductions in patients who experienced toxicity from treatment. If toxicity recurred after a second dose reduction, ZYNLONTA was discontinued permanently.[2] Please note that protocol guidelines reflect knowledge at the time LOTIS-2 was initiated and differ from the guidelines provided in the ZYNLONTA Prescribing Information, which are based on additional information gleaned from the LOTIS-2 results. Review of the ZYNLONTA Prescribing Information is recommended.

## Literature Search

- A PubMed biomedical literature search conducted on February 28, 2025, yielded no further relevant data regarding the incidence of thrombocytopenia with ZYNLONTA.

## Relevant Prescribing Information

*Section 2: Dosage and Administration*[8]

*2.3 Dosage Delays and Modifications*

**Table 4: Dose Delays and Modifications.** Adapted from Prescribing Information.[8]

| Adverse Reactions | Severity[a] | Dosage Modification |
|---|---|---|
| **Hematologic Adverse Reactions** | | |
| **Thrombocytopenia (see Warnings and Precautions [5.2])** | Platelet count less than 50,000/mcL | Withhold ZYNLONTA until platelet count returns to 50,000/mcL or higher |

- 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: Warnings and Precautions*[8]

*5.2 Myelosuppression*[8]

- Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3% [*see Adverse Reactions (6.1)*].
- Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony stimulating factor administration as applicable [*see Dosage and Administration (2.3)*].

*Section 6: Adverse Reactions*[8]

*6.1 Clinical Trials Experience*

- In the pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma- glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

*Relapsed or Refractory Diffuse Large B-Cell Lymphoma*[8]

- All grade platelets decrease was reported in 58% of patients receiving ZYNLONTA in LOTIS-2, while Grade 3 or 4 platelets decrease was reported in 17% of patients.
- Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma- glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

## References


[1] 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

[2] Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2021 Jun;22(6):790-800. doi: 10.1016/S1470-2045(21)00139-X

[3] Data on File. LOTIS-1 Clinical Study Report. ADC Therapeutics.

[4] Kahl BS, Hamadani M, Caimi F, et al. LOTIS-2 follow-up analysis: Updated results from a Phase 2 study of loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma. Poster presented at: the Society of Hematologic Oncology (SOHO) Virtual Congress; September 8–11, 2021.

[5] Caimi PF, Ai W, Alderuccio JP, et al. Efficacy and safety of loncastuximab tesirine (ADCT-402) in relapsed/refractory diffuse large B-cell lymphoma. Presented at American Society of Hematology (ASH) Virtual Congress; December 5, 2020.

[6] Data on File. LOTIS-2 Clinical Study Report. ADC Therapeutics.

[7] 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. Haematol. Published online August 31, 2023. doi: 110.3324/haematol.2023.283459

[8] ZYNLONTA® (loncastuximab tesirine-lpyl) FDA-approved Prescribing Information. October 2022




**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**