ZYNLONTA® (loncastuximab tesirine-lpyl) – Incidence and Management of Edema, Effusion and Capillary Leak Syndrome

Summary

- Incidences of edema and/or effusion are considered likely related to the pyrrolobenzodiazepine (PBD) component of ZYNLONTA.[3]
- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study which evaluated the safety and tolerability of ZYNLONTA monotherapy in 183 adult patients with relapsed or refractory B-cell Non-Hodgkin Lymphoma (R/R B-NHL).[1]
    - In the safety analysis set of R/R B-NHL patients, some of the all-grade treatment-emergent adverse events (TEAEs) were peripheral edema 58 (31.7%), pleural effusion 39 (21.3%), pericardial effusion 11 (6.0%), facial edema 10 (5.5%), and ascites 1 (0.5%) in all doses combined.[1,2]
    - Among the subgroup of diffuse large B-cell lymphoma (DLBCL) safety analysis set, some of the all-grade TEAEs were peripheral edema 46 (33.1%), pleural effusion 30 (21.6%), facial edema 8 (5.8%), and pericardial effusion 8 (5.8%). There was no incidence of ascites in the DLBCL subgroup.[2]
- LOTIS-2 was a pivotal phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA monotherapy in adult patients with R/R DLBCL following ≥2 lines of prior systemic therapy.[3]
    - Edema includes edema, face edema, generalized edema, peripheral edema, ascites, fluid overload, peripheral swelling, swelling, and swelling face.[6]
    - TEAEs in the all-treated population included peripheral edema 29 (20%), pleural effusion 15 (10.3%), facial edema 7 (4.8%), localized edema 6 (4.1%), ascites 5 (3.4%), pericardial effusion 4 (2.8%), swelling 4 (2.8%), peripheral swelling 3 (2.1%), fluid overload 1 (0.7%), and generalized edema 1 (0.7%).[3,7]
    - Patients were given premedication with dexamethasone unless contraindicated to help prevent any PBD related adverse events.[3,6.]
    - Spironolactone at standard doses were administered for patients with weight gain greater than 1 kg from Cycle 1 Day 1, new or worsening edema, and/or new or worsening pleural effusion. The dose of spironolactone could be titrated as clinically indicated. Additional diuretic support could be added if there was further increase in weight, edema, or pleural effusion.[7]
- As of data cut off April 6, 2020, the incidence of any Grade edema and Grade ≥3 edema was 40 (27.6%) and 5 (3.4%) respectively. The incidence of any Grade effusion and Grade ≥3 effusion was 16 (11%) and 4 (2.8%), respectively.[6]
    - The median duration of any Grade edema and effusion was 50.5 and 19.5 days, respectively, and the median duration of Grade ≥3 edema and effusion was 5 days and 20.5 days, respectively.
- Serious effusion and edema, including capillary leak syndrome, have occurred in patients treated with ZYNLONTA. In the pooled safety population, Grade 3 edema occurred in 3%, Grade 3 pleural effusion in 3%, Grade 3 or 4 pericardial effusion in 1%, and Grade ≥3 capillary leak syndrome in 0.6%. Rare cases of cardiac tamponade have been reported.[8]

- If the patient experiences Grade ≥2 edema or effusion, withhold ZYNLONTA until toxicity resolves to Grade ≤1.[8]
- If the patient experiences Grade 2 pericardial effusion, withhold ZYNLONTA until toxicity resolves, discontinue ZYNLONTA if effusion recurs.[8]
- If the patient experiences Grade ≥3 pericardial effusion, discontinue ZYNLONTA.
- 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.[8]
- See **Relevant Prescribing Information** for additional information regarding dose delays/reduction.

Clinical Data

LOTIS-1 (Phase 1)[1]

- LOTIS-1 was the first-in-human phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study that evaluated the safety and tolerability of ZYNLONTA, used as monotherapy, in adult patients with R/R B-NHL.
    - The primary objectives of Part 1 were to evaluate the safety and tolerability of ZYNLONTA and to determine the MTD and recommended dose(s) for Part 2. The primary objective of Part 2 was to evaluate safety and tolerability at the recommended dose(s).
- In Part 1, 88 patients received treatment with ZYNLONTA at doses of 15-200 µg/kg every 3 weeks (Q3W). During part 2 of the study, 26 patients received ZYNLONTA 120 µg/kg Q3W and 69 patients received 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 seen at the 200 µg/kg dose and evidence of activity at 120 and 150 µg/kg dose during Part 1.
- In the safety analysis set, 183 patients (Part 1 + Part 2), 181 patients (98.9%) experienced at least one treatment-emergent adverse event (TEAE). The rates of all-grades peripheral edema, pleural effusion, pericardial effusion, and ascites in specific dose cohorts and combined across the dose cohorts are summarized in Table 1.

Table 1. Treatment-Emergent Adverse Events (TEAE) by Preferred Term, Safety Analysis Set. Adopted from Data on File.[2]

TEAE, n (%)	Dose (µg/kg)				
	≤90	120	150	200	All Doses
Preferred Term	**Part 1 (n=17)**	**Part 1+2 (n=42)**	**Part 1+2 (n=88)**	**Part 1 (n=36)**	**(N=183)**
Any TEAE	16 (94.1)	42 (100)	87 (98.9)	36 (100)	181 (98.9)
Peripheral edema	1 (5.9)	12 (28.6)	31 (35.2)	14 (38.9)	58 (31.7)
Pleural effusion	2 (11.8)	10 (23.8)	19 (21.6)	8 (22.2)	39 (21.3)
Pericardial effusion	1 (5.9)	3 (7.1)	4 (4.5)	3 (8.3)	11 (6.0)
Ascites	0 (0)	0 (0)	0 (0)	1 (2.8)	1 (0.5)

- Incidence of edema and effusion reduced in Part 2 after introduction of dexamethasone premedication.[1]

- Following the introduction of dexamethasone premedication, the incidence of edema or effusion was reduced in Part 2 (120 µg/kg: 34.6%; 150 µg/kg: 47.8%) compared to Part 1 (120 µg/kg: 68.8%; 150 µg/kg: 63.2%).[1]
- There were no reports of Grade 5 or fatal edema or effusion related events.
- See Table 2 below for an overview of the incidence of edema and effusion in DLBCL patients.

Table 2. TEAEs by Preferred Term, for DLBCL Patients (Safety Analysis Set). Adopted from Data on File.[2]

TEAE, n (%)	Dose (µg/kg)				
	≤90	120	150	200	All Doses
Preferred Term	**Part 1 (n=10)**	**Part 1+2 (n=32)**	**Part 1+2 (n=70)**	**Part 1 (n=27)**	**(N=139)**
Patients with Any TEAE	10 (100)	32 (100)	69 (98.6)	27 (100)	138 (99.3)
Peripheral edema	1 (10)	10 (31.3)	24 (34.3)	11 (40.7)	46 (33.1)
Pleural effusion	1 (10)	8 (25)	15 (21.4)	6 (22.2)	30 (21.6)
Pericardial effusion	0 (0)	3 (9.4)	3 (4.3)	2 (7.4)	8 (5.8)
Facial Edema	0 (0)	3 (9.4)	3 (4.3)	2 (7.4)	8 (5.8)

LOTIS-2 (Phase 2)[3]

- LOTIS-2 was a pivotal phase 2, multicenter, open-label single-arm study that evaluated the efficacy and safety of ZYNLONTA used as monotherapy in adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) following ≥2 lines of prior systemic therapy. The primary endpoint was overall response rate assessed by central review.
    - Out of the 145 patients, 143 patients (99%) experienced at least one TEAEs.
- Patients with clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath) were excluded from the study.[4]

Edema or Effusion

- Edema or effusion was reported in 45 patients (31%) and the incidence of each individual event may be seen in Table 3 below.[3]
    - Edema includes edema, face edema, generalized edema, peripheral edema, ascites, fluid overload, peripheral swelling, swelling, and swelling face.[6]
    - There were no reports of Grade 5 or fatal edema or effusion related events; however, there was one report of Grade 4 pericardial effusion.

Table 3. Selected TEAEs by Preferred Term (All-Treated Population). Adopted from Caimi and Date on File.[3,7]

Preferred Term	Grades 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)
Edema or Effusion	38 (26.2)	6 (4.1)	1 (0.7)	45 (31)
Peripheral Edema	27 (18.6)	2 (1.4)	0 (0)	29 (20)
Pleural Effusion	12 (8.3)	3 (2.1)	0 (0)	15 (10.3)
Face Edema	6 (4.1)	1 (0.7)	0	7 (4.8)
Localized Edema	6 (4.1)	0	0	6 (4.1)
Ascites	2 (1.4)	3 (2.1)	0 (0)	5 (3.4)
Swelling	4 (2.8)	0	0	4 (2.8)

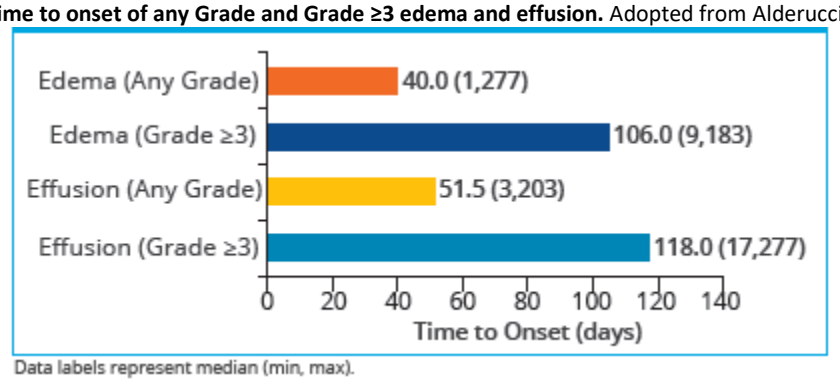
Peripheral Swelling	3 (2.1)	0	0	3 (2.1)
Fluid Overload	1 (0.7)	0	0	1 (0.7)
Generalized Edema	1 (0.7)	0	0	1 (0.7)

- The most common adverse events leading to treatment discontinuation were increased gamma-glutamyl transferase (15 [10%] of 145 patients), peripheral edema (four [3%]), localized edema (three [2%]), and pleural effusion (three [2%]).[3]
- As of a recent data cut-off of March 01, 2021, all-grade TEAE of edema or effusion was reported in 45 patients (31%).[5]
    - These TEAEs are considered likely related to the PBD component of ZYNLONTA.

Incidence, Onset, and Duration

- As of data cut off April 6, 2020, the incidence of any Grade edema and Grade ≥3 edema was 40 (27.6%) and 5 (3.4%) respectively. The incidence of any Grade effusion and Grade ≥3 effusion was 16 (11%) and 4 (2.8%), respectively.[6]
    - Any Grade edema and effusion typically developed within the first 3 treatment cycles, while Grade ≥3 edema and effusion typically developed within the first 6 treatment cycles. See Figure 1 below for additional information.

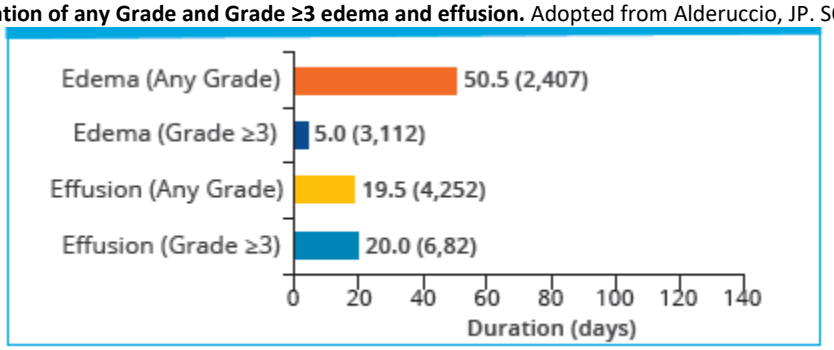
Figure 1: Median time to onset of any Grade and Grade ≥3 edema and effusion. Adopted from Alderuccio, JP. SOHO 2021.[6]



Data labels represent median (min, max).

- The median duration of any Grade edema and effusion was 50.5 and 19.5 days, respectively, and the median duration of Grade ≥3 edema and effusion was 5 days and 20.5 days, respectively.[6] See Figure 2 below for additional information.

Figure 2: Median duration of any Grade and Grade ≥3 edema and effusion. Adopted from Alderuccio, JP. SOHO 2021.[6]



Data labels represent median (min, max).

Management of Edema & Effusion, including CLS

- In LOTIS-2, unless contraindicated, the protocol mandated dexamethasone 4 mg orally twice daily the day before ZYNLONTA administration (if possible), the day of ZYNLONTA administration (give at least 2 hours prior to administration when not given the day before; otherwise, any time prior to administration), and the day after ZYNLONTA administration.[7]
    - This intervention was given to reduce the incidence of edema/effusion when implemented in Phase 1; data from Phase 2 was consistent with this intervention.
    - Patients were instructed to report signs and symptoms of edema such as peripheral swelling or unexplained weight gain. They were advised to monitor their weight daily, at around the same time (preferably in the morning), and to report a weight increase of greater than 1 kg over baseline to the investigator.[4]
    - Diagnostic imaging was considered in patients who developed symptoms of pleural effusion, pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.[8]
    - Evaluate and initiate appropriate medical management for CLS in patients who develop worsening effusion or edema accompanied by signs and symptoms such as weight gain, severe hypotension, hypoalbuminemia, and/or hemoconcentration (e.g., elevated hemoglobin or hematocrit). Withhold or permanently discontinue ZYNLONTA based on the severity of the event.[8]
    - Diuretic therapy (bumetanide, furosemide, or spironolactone) was administered to 20 (50%) of the patients with edema. The median time from the first dose of ZYNLONTA to the start of diuretic therapy for edema was 93 days.[6]
    - Diuretic therapy for the treatment of effusion was administered to 7 (43.8%) of the patients with effusion. The median time from the first dose of ZYNLONTA to the start of diuretic therapy for effusion was 87 days.[6]
- Adverse events including edema and effusion were managed by a dose delay of ZYNLONTA followed by a subsequent dose reduction of 50% in addition to supportive care.[3,7]
    - Dose delays, reductions, and discontinuations occurred due to effusion in 11.8%, 0%, and 23.5% of patients who experienced effusions (n=17), respectively.[5]
    - Dose delays, reductions, and discontinuations occurred due to edema in 17.5%, 2.5%, and 10% of patients who experienced edema (n=40), respectively.[5]
- Initial recommended treatment for new or worsening edema and/or new or worsening pleural effusion was to administer spironolactone at standard doses for patients with weight gain greater than 1 kg (2.2lbs) from Cycle 1 Day 1.[1,2]
    - Dose of spironolactone could be titrated as clinically indicated.
    - Additional diuretic support could be added if there was further increase in weight, edema, or pleural effusion.
    - Loop diuretics were not observed to be effective in mitigating edema/effusion.

Literature Search

- A PubMed biomedical literature search conducted on February 27, 2026, yielded no relevant data regarding the Incidence and Management of Edema and Effusion with ZYNLONTA.

Relevant Prescribing Information

Section 2: Dosage and Administration[8]

2.3: Dose Delays and Modifications

Table 1: Dose Delays and Modifications. Adopted from Prescribing Information.[8]

Adverse Reaction	Severity[a]	Dosage Modification
Nonhematologic Adverse Reactions		
Edema or Effusion [see Warnings and Precautions (5.1)]	Grade 2[a] or higher	Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less
Pericardial Effusion [see Warnings and Precautions (5.1)]	Grade 2 Grade 3 or higher	Withhold ZYNLONTA until the toxicity resolves. Discontinue ZYNLONTA if effusion recurs. Discontinue ZYNLONTA

[a]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: Warnings and Precautions[8]

5.1: Effusion and Edema, Including Capillary Leak Syndrome

- Serious effusion and edema, including capillary leak syndrome, occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3%, and Grade 3 or 4 pericardial effusion occurred in 1% [see Adverse Reactions (6.1)].
- Rare cases of cardiac tamponade have been reported in patients with Grade 3 or 4 pericardial effusion. Grade 3 or higher capillary leak syndrome occurred in 0.6%.
- Monitor patients for new or worsening edema or effusions. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.
- Evaluate and institute appropriate medical management for capillary leak syndrome in patients experiencing worsening effusion or edema, with signs and symptoms of weight gain, severe hypotension, hypoalbuminemia, and/or hemoconcentration (by elevated hemoglobin/hematocrit, etc.)
- Withhold or discontinue ZYNLONTA based on severity [see Dosage and Administration (2.3)].

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;137(19):2634-2645. doi:10.1182/blood.2020007512

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

[3] 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

[4] 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 [supplementary appendix]. *Lancet Oncol*. 2021;22(6):790-800. doi:10.1016/S1470-2045(21)00139-X

[5] Grandas, et al. Onset, Duration, and Management of Edema and Effusion in Patients treated With Loncastuximab Tesirine for R/R/ DLBCL: Updated Results from the LOTIS-2 Clinical Trial. Poster presented at: 47th Annual ONS Congress. April 27-May 1, 2022

[6] Alderuccio, JP, Ardeshna K, et al. Incidence, onset, and management of edema and effusion in patients treated with loncastuximab tesirine for R/R DLBCL in the LOTIS clinical trial program. Poster presented at: Society of Hematologic Oncology (SOHO) Virtual Congress; September 8-11, 2021; Virtual

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

[8] ZYNLONTA® (loncastuximab tesirine-lpyl) for injection Prescribing Information, February 2026

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.