ZYNLONTA® (loncastuximab tesirine-lpyl) – Pharmacokinetics

Summary

- 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 145 adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) following ≥2 lines of prior systemic therapy.[1]
    - Pharmacokinetic parameters (loncastuximab tesirine total antibody, pyrrolobenzodiazepine-conjugated antibody, and SG3199 [unconjugated payload] in serum) were analyzed using validated electrochemiluminescence immunoassays (ECLIA) and liquid chromatography-tandem mass spectrometric assay.[1]
- The *in vitro* plasma protein binding of SG3199 appeared high, the free fraction ranging from 5-5.9% (~94% plasma protein bound).[2,3]
- ZYNLONTA is approved to be administered as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer intravenous infusion as follows:[5]
    - 0.15 mg/kg every 3 weeks for 2 cycles.
    - 0.075 mg/kg every 3 weeks for subsequent cycles.
    - For patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW) as follows: ABW in kg = 35 kg/m^2 × (height in meters)^2
- See Relevant Prescribing Information for additional information.

Nonclinical Data

- The *in vitro* binding of [^{3}H]-SG3199 to plasma proteins were evaluated in rat (Sprague Dawley), monkey (Cynomolgus) and human by equilibrium dialysis at the concentrations of 0.8, 0.5, and 50 ng/mL.[3]
    - The plasma protein binding of SG3199 appeared high in all species. The free fractions according to the lowest and highest concentration were monkey (10.5-6.4%) > human (5-5.9%) > rat (2.8-2.8%).
- The plasma protein binding did not appear to be concentration dependent, however the free fraction increased marginally at the target concentration of 5 ng/mL.[3]
- The free fraction at 5 ng/mL ranked as: humans (11.4%) > monkey (10.7%) > rat (7.7%).[3]

Clinical Data

- Pharmacokinetic parameters (loncastuximab tesirine total antibody, pyrrolobenzodiazepine-conjugated antibody, and SG3199 [unconjugated payload] in serum) were analyzed using validated electrochemiluminescence immunoassays (ECLIA) and liquid chromatography-tandem mass spectrometric assay.[1]
- See Table 1 below for additional pharmacokinetic parameters for the conjugated antibody, total antibody, and SG3199.

Table 1: Summary of pharmacokinetic parameters during Cycle 1, 2, and 3 for patients with evaluable and sufficient concentration-time data. Adopted from Caimi PF, et al. Supplement.[4]

Analyte	Cycle	Dose (µg/kg)	C_{max} (ng/mL)	AUC_{last} (day*ng/mL)	AUC (day*ng/mL)	T_{half} (day)	CL (L/day)	V_{ss} (L)	AI
Conjugated Antibody*	1	150	2430 (38.8) [142]	15850 (105) [143]	19825 (52.9) [32]	8.85 (53.5) [32]	0.458 (47.6) [32]	4.24 (39.6) [32]	N/A
	2	150	2734 (35.8) [117]	23913 (67.1) [116]	26902 (33.4) [99]	15.2 (31.7) [90]	0.331 (32) [99]	6.4 (36.5) [90]	1.65 (18.5) [90]
	3	75	1694 (47.6) [83]	N/A	N/A	N/A	N/A	N/A	N/A
Total Antibody†	1	150	3267 (36.7) [142]	22160 (106) [143]	25778 (61.3) [27]	8.66 (54.6) [27]	0.418 (56.5) [27]	4.1 (36.4) [27]	N/A
	2	150	3756 (31.3) [117]	33762 (67.2) [116]	37761 (30.4) [97]	20.9 (56.5) [63]	0.285 (31.3) [97]	7.54 (58.9) [63]	2.07 (38.1) [63]
	3	75	2581 (41.9) [81]	N/A	N/A	N/A	N/A	N/A	N/A
SG3199	1	150	0.041 (56.6) [8]	0.004 (576) [8]	N/A	N/A	N/A	N/A	N/A
	2	150	0.049 (78.8) [5]	0.001 (204) [5]	N/A	N/A	N/A	N/A	N/A
	3	75	0.032 (20.3) [3]	N/A	N/A	N/A	N/A	N/A	N/A

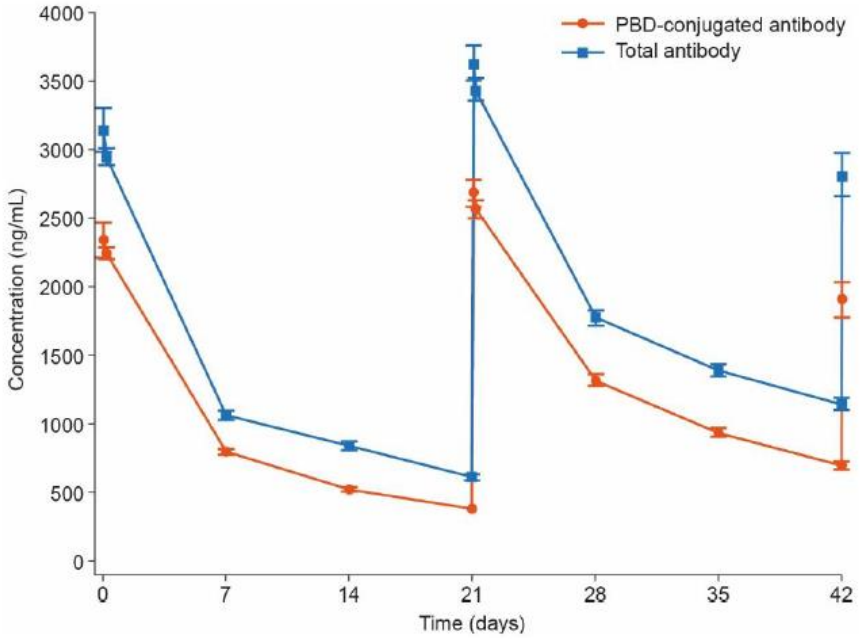
Data presented as geometric mean (CV %) [N]. Only end-of-infusion concentration (C_{max}) was reported for Cycle 3 given the limited sampling at predose and end of infusion.

*Drug-to-antibody ratio (DAR) ≥1; † DAR≥0

AI, accumulation index; AUC, area under the concentration-time curve from time 0 to infinity for Cycle 1 and area under the concentration-time curve from time 0 to end of dosing interval for Cycle 2; AUC_{last}, area under the concentration-time curve from time 0 to last measurable time point in respective cycle; C_{max}, maximum observed concentration for Cycles 1 and 2 or concentration at end-of-infusion for Cycle 3; CL, apparent clearance for Cycle 1 and apparent clearance at steady state for Cycle 2; CV%, geometric percent coefficient of variation; N, number of patients; N/A, not available; T_{half}, apparent terminal half-life; V_{ss}, apparent volume of distribution at steady state.

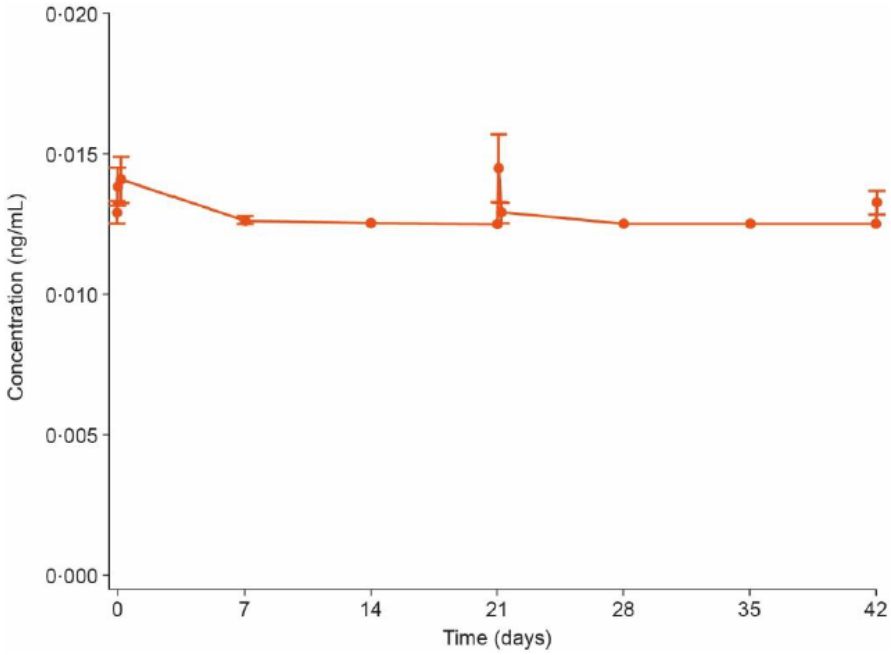
- Figure 1 below shows the concentration of conjugated antibody and total antibody in serum versus time and Figure 2 shows the concentration of SG3199 in serum versus time.

Figure 1: Mean (±SE) concentration of loncastuximab tesirine PBD-conjugated antibody and total antibody in serum versus time for patients during Cycles 1, 2, and 3. Adopted from Caimi PF, et al. Supplement.[4]



Values below LLOQ of conjugated antibody (LLOQ=5·06 ng/mL) and total antibody (LLOQ=20 ng/mL) were set as LLOQ/2, respectively.
LLOQ, lower limit of quantification; PBD, pyrrolobenzodiazepine; SE, standard error.

Figure 2: Mean (±SE) concentration of loncastuximab tesirine SG3199 in serum versus time for patients during Cycles 1, 2, and 3. Adopted from Caimi PF, et al. Supplement.[4]



Values below LLOQ of SG3199 (LLOQ=0·025 ng/mL) were set as LLOQ/2. Loncastuximab tesirine was administered on Days 1, 21, and 42.
LLOQ, lower limit of quantification; SE, standard error.

Literature Search

- A PubMed biomedical literature search conducted on November 3, 2025, yielded no further relevant data regarding the pharmacokinetics of ZYNLONTA.

Relevant Prescribing Information

Section 12: Clinical Pharmacology[5]

12.3 Pharmacokinetics

- The exposure of loncastuximab tesirine-lpyl at the approved recommended dosage in Cycle 2 and at steady state is shown in Table 2. Loncastuximab tesirine-lpyl steady state C_{max} was 28.2% lower than the C_{max} after the first dose. The time to reach steady state was 105 days.

Table 2: Loncastuximab Tesirine-lpyl Exposure Parameters.[a] Adopted from Prescribing Information.[5]

Time	C_{max} (ng/mL)	AUC_{tau} (ng*day/mL)
Cycle 2	2,911 (35.3%)	21,665 (54.1%)
Steady State	1,776 (32.1%)	16,882 (38.2%)

C_{max} = Maximum observed serum concentration; AUC_{tau} = Area under curve over the dosing interval

[a]Data presented as mean and coefficient of variation (CV%)

Distribution

- The mean (CV%) of loncastuximab tesirine-lpyl volume of distribution was 7.11 (26.6%) L.

Elimination

- The mean (CV%) of loncastuximab tesirine-lpyl clearance decreased with time from 0.499 L/day (89.3%) after a single dose to 0.275 L/day (38.2%) at steady state. The mean (standard deviation) half-life of loncastuximab tesirine-lpyl was 20.8 (7.06) days at steady state.

Metabolism

- The monoclonal antibody portion of loncastuximab tesirine-lpyl is expected to be metabolized into small peptides by catabolic pathways. The small molecule cytotoxin, SG3199, is metabolized by CYP3A4/5 in vitro.

Excretion

- The major excretion pathways of SG3199 have not been studied in humans. SG3199 is expected to be minimally renally excreted.

Specific Populations

- No clinically significant differences in the pharmacokinetics of loncastuximab tesirine-lpyl were observed based on age (20-94 years), sex, race (White vs. Black), body weight (42.1 to 160.5 kg), ECOG status (0 to 2) or mild to moderate renal impairment (CLcr 30 to <90 mL/min using the Cockcroft-Gault equation).
- The effect of severe renal impairment (CLcr 15 to 29 mL/min), and end-stage renal disease with or without hemodialysis on loncastuximab tesirine-lpyl pharmacokinetics is unknown.

Patients with Hepatic Impairment

- Mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 × ULN and any AST) may increase the exposure of unconjugated SG3199, however there was no clinically significant effect on loncastuximab tesirine-lpyl pharmacokinetics. The effect of moderate (total bilirubin >1.5 to ≤3 × ULN and any AST) or severe (total bilirubin >3 ULN and any AST) hepatic impairment on loncastuximab tesirine-lpyl pharmacokinetics is unknown.

Drug Interaction Studies

In Vitro Studies

- *Cytochrome P450 (CYP) Enzymes*: SG3199 does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 at clinically relevant unconjugated SG3199 concentrations.
- *Transporter Systems*: SG3199 is a substrate of P-glycoprotein (P-gp), but not a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP)1B1, or organic cation transporter (OCT)1.
- SG3199 does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, OCT2, OCT1, multi-antimicrobial extrusion protein (MATE)1, MATE2-K, or bile salt export pump (BSEP) at clinically relevant unconjugated SG3199 concentrations.

References

[1] 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
[2] Data on File, Plasma Protein Binding Memo. ADC Therapeutics.
[3] Data on File, The *In Vitro* Plasma Protein Binding and Blood Cell partitioning of [^{3}H]-SG3199 in Rat, Monkey, and Human. ADC Therapeutics.
[4] Caimi PF, Weiyun A, 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 May 11. DOI: 10.1016/S1470-2045(21)00139-X.
[5] ZYNLONTA® (loncastuximab tesirine-lpyl) for injection 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.