Crisantaspase (Enrylaze®) for the treatment of acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL)

General information

Drug description [1]

The active substance of Enrylaze® is crisantaspase[1], an antineoplastic agent. Crisantaspase catalyses the conversion of L-asparagine into L-aspartic acid and ammonia. Depletion of asparagine in blood serum results in apoptosis of cells highly dependent on asparagine, especially leukaemic blasts.

Indication [1]

Crisantaspase (Enrylaze®) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL and LBL in adult and paediatric patients (1 month and older) who developed hypersensitivity or silent inactivation to E. coli-derived asparaginase.

The differentiation of ALL and LBL is made by the percentage of blasts among the bone marrow (cut off 25%) [3].

Incidence

The overall incidence of ALL is 1.1 per 100,000 persons per year. The peak incidence is in childhood at the age of <5 years (5.3/100,000); afterward, the incidence decreases continuously. In Patients >50 years of age, incidence slowly increases again until a second peak incidence at the age of > 80 years (2.3/100,000) [2].

Current treatment [3]

- ❖ In patients with peg-asparaginase activity <50 U/l even on day 7 after administration of 2000 U/m^2 the occurrence of a silent inactivation can be assumed. Hence, the continued administration of peg-asparaginase is no longer reasonable.
- ❖ To achieve further asparagine depletion and thereby an anti-leukaemic effect, it should be changed over to Erwinase therapy. After the change, peg-asparaginase activity measures have to be continued, aiming to establish if asparaginase-activity >50 U/l (over a comparable period of time) can be achieved.

Regulatory status

EMA [1]

Approval status for this indication: On 20 July 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for **Enrylaze®**.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 15/09/2023

The full indication is:

- ❖ Enrylaze® is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL and LBL in adult and paediatric patients (1 month and older) who developed **hypersensitivity or silent inactivation** to E. coli-derived asparaginase.

Other indications: none

- ✓ Medicine is under additional monitoring

FDA [4]

Approval status for this indication: On 30 June 2021, the FDA approved asparaginase Erwinia chrysanthemi (recombinant)-rywn) (**Rylaze®**) as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL and LBL in adult and paediatric patients 1 month or older who have developed **hypersensitivity** to E. coli-derived asparaginase.

- ✓ Fast track
- ✓ Orphan drug designation

Other indications: none

Manufacturer [5]

Enrylaze® and Rylaze® are manufactured by Jazz Pharmaceuticals Inc.

[1] Also known as Erwinia asparaginase.

Costs

Currently, there is no cost information available.

Posology [6]

Recommended premedication

- A consideration to premedicate patients with paracetamol, an H1 receptor blocker, and an H2 receptor blocker 30–60 minutes prior to administration should be made when Enrylaze® is being given intravenously to decrease the risk and severity of infusion related reaction/hypersensitivity reaction.

Recommended monitoring

- Asparaginase activity can vary between individuals, therefore trough SAA should be monitored. When administered every 48 hours a trough asparaginase activity measurement should be performed at
  48 hours post dose. When dosing on a Monday/Wednesday/Friday schedule, trough SAA should be measured 72 hours after the Friday dose and prior to administration of the following Monday dose.
- The dosing schedule or route of administration should then be individually adapted.

Warnings and precautions [5, 6]

- **Hypersensitivity**
  - Monitor for signs or symptoms. Discontinue Rylaze® for serious reaction.
- **Pancreatitis**
  - Monitor for symptoms. Discontinue if pancreatitis occurs.
- **Thrombosis**
  - Discontinue Rylaze® for severe or life-threatening thrombosis. Provide anticoagulation therapy as indicated.
- **Haemorrhage**
  - Discontinue Rylaze® for severe or life-threatening haemorrhage.
- **Hepatotoxicity**
  - Discontinue Rylaze® for grade 4 increases of bilirubin.
- Traceability
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- Clinical monitoring
  - Asparaginase activity
    - SAA varies substantially between patients, when treatment is administered intravenously. The optimal SAA level is ≥ 0.1 U/mL; if this is not observed the dosing schedule should be individually adapted.
    - When administering Enrylaze intravenously on a Monday/Wednesday/Friday schedule, trough SAA levels should be measured 72 hours after the Friday dose and prior to the following Monday administration. If SAA levels ≥ 0.1 U/mL are not observed, administration of intramuscular Enrylaze® or switching to a 48-hour dosing interval (intravenous or intramuscular) should be considered. If SAA levels are monitored at 48-hour intervals of intravenous Enrylaze administration and SAA levels ≥ 0.1 U/mL are not observed, administration intramuscularly should be considered.
- Glucose intolerance
  - Cases of glucose intolerance have been reported in patients receiving Enrylaze in clinical trials. Glucose levels in patients should be monitored at baseline and periodically during treatment. Insulin therapy should be administered as necessary in patients with hyperglycaemia.
- Neurotoxicity
  - Central nervous system (CNS) toxicity, including encephalopathy, seizures and CNS depression as well as posterior reversible encephalopathy syndrome (PRES) may occur during treatment with any asparaginase therapy. PRES may occur rarely during treatment with any asparaginase. This syndrome is characterised in magnetic resonance imaging (MRI) by reversible (from a few days to months) lesions/oedema, primarily in the posterior region of the brain.

- Symptoms of PRES essentially include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily cortical blindness or homonymous hemianopsia).
- It is unclear whether the PRES is caused by asparaginase, concomitant treatment or the underlying diseases. PRES is treated symptomatically, including measures to treat any seizures. Discontinuation or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary. Expert advice should be sought.

❖ Contraception
- Contraception should be used during treatment and for 3 months after receiving the final dose of Enrylaze®. Women should also undergo pregnancy testing before therapy with Enrylaze® is initiated.
- Since an indirect interaction between oral contraceptives and Enrylaze cannot be ruled out, patients of childbearing potential should use effective non-hormonal contraceptive methods while undergoing treatment.

❖ Sodium content
- This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say, essentially 'sodium-free'

Study characteristics [7, 8]

Trial name	*n*	Intervention (I), Cohort 1a (n=33)	Intervention2 (I2), cohort 1b (n=83)	Comparator (C), cohort 1c (n=51)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
AALL1931 NCT04145531	167[2]	6 doses of IM JZP458[3] 25 mg/m^2 on MWF[4]	6 doses of IM JZP458 37.5 mg/m2 on MWF	6 doses of IM JZP458 25/25/50 mg/m2 on MWF	Proportion of patients with the last 72-hour NSAA level ≥0.1 IU/mL	NA	Pivotal, open-label, multi-centre, multi-cohort, dose-confirmation, pharmacokinetic, phase 2/3 study	-	Jazz Pharmaceuticals	AALL1931 trial [7]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (Cohort 1a vs. 1b vs. 1c)
❖ Paediatric or adult patients with ALL or LBL were eligible if they reported a grade ≥3 allergic reaction to a long-acting Escherichia coli–derived asparaginase or silent inactivation, defined as a nadir serum asparaginase activity (NSAA) level <0.5 IU/mL between the time point of 1 hour and 1 day post dose, <0.3 IU/mL within 7 days post dose, or <0.1 IU/mL within 14 days post dose ❖ Patients had ≥1 course of E. coli-derived asparaginase remaining in the treatment plan; had fully recovered from the prior allergic reaction; had undetectable SAA levels based on the lower limit of quantitation, as defined by a certified laboratory authorised under Clinical Laboratory Improvement Amendments at enrolment if the	❖ Patients who previously received Erwinia-derived asparaginase or JZP458 ❖ Patients who had relapsed ALL/LBL ❖ History of grade ≥3 pancreatitis or asparaginase-associated haemorrhagic event	❖ Median age, years (range): 11 (1-24) vs. 8 (1-20) vs. 12 (3-25) ❖ Male sex: 52% vs. 66% vs. 61% ❖ Median BMI, kg/m^2: 19.9 vs. 17.9 vs. 18.4 ❖ Median BSA, m^2: 1.28 vs. 1.01 vs. 1.29 ❖ Primary disease: • ALL o B-ALL: 82% vs. 72% vs. 73% o T-ALL: 12% vs. 16% vs. 18% • LBL o B-LBL: 0 vs. 0 vs. 2% o T-LBL: 6% vs. 12% vs. 8%

[2] Cohort 1a (n = 33), cohort 1b (n = 83), and cohort 1c (n = 51). Each remaining pegylated E. coli–derived asparaginase dose on a patient's treatment plan was replaced by 1 course of IM JZP458 (6 doses administered on a MWF schedule over 2 weeks), with the initial dose starting on M, W, or F, to align with the patient's planned chemotherapy schedule. All other chemotherapy continued according to the original treatment protocol for the patient's ALL/LBL.

[3] JZP458 = asparaginase Erwinia chrysanthemi (recombinant)-rywn

[4] Monday/Wednesday/Friday

patient received ≥10% of an E. coli-derived asparaginase intravenous infusion prior to allergic reaction ❖ Adequate liver function, defined as direct bilirubin ≤3 × ULN, and alanine aminotransferase and aspartate aminotransferase ≤5 × ULN		❖ Eligibility criteria met: • Grade ≥3 allergic reaction to an Escherichia coli–derived asparaginase[5]: 82% vs. 90% vs. 86% • Silent inactivation: 9% vs. 4% vs. 2% • Allergic reaction with inactivation: 9% vs. 6% vs. 12%

Efficacy (I vs. C)	**Safety** (I vs. C)
❖ Following the first treatment course of JZP458, the proportion (95% CI) of patients who achieved NSAA levels ≥0.1 IU/mL at 72 hours was 64% (47%-82%) in cohort 1a vs. 91% (84%-97%) in cohort 1b vs. 90% (81%-98%) in cohort 1c. ❖ At 48 hours, >95% of patients in each cohort (cohort 1a: 97% (91%-100%); cohort 1b: 99% (96%-100%); and cohort 1c: 96% (90%-100%) achieved NSAA levels ≥0.1 IU/mL. ❖ The mean (IQR 25-75) NSAA levels at 72 hours were 0.16 (0.09-0.23) in cohort 1a vs. 0.33 (0.17-0.41) in cohort 1b vs. 0.47 (0.17-0.59) in cohort 1c. ❖ At 48 hours, mean NSAA levels were 0.45 (0.27-0.65) in cohort 1a vs. 0.88 (0.47-1.09) in cohort 1b vs. 0.66 (0.33-0.89) in cohort 1c. **PopPK modelling and simulations** ❖ The clinical efficacy of JZP458 was demonstrated by a combination of observed data and modelled results, which included observed NSAA levels at the protocol-specified time points and PopPK modelling and simulation results. ❖ The PopPK model that best described the PK (based on SAA) of JZP458 following IM administration was a 1-compartment IM model with mixed-order absorption and linear elimination, with body surface area included as an allometric covariate on JZP458 SAA clearance and volume of distribution, accompanied with self-reported race and disease subtype as categorical covariates on JZP458 SAA clearance. ❖ This model indicated that the simulated proportion of patients achieving NSAA ≥0.1 IU/mL exceeded 90% in both Black/African American and non-Black/African American patients, suggesting that no clinically significant difference would be expected in patients following the proposed BSA–based dosing. Therefore, no dose modification is recommended on the basis of ethnicity, including African American patients. ❖ Using this PopPK model, simulations suggested that when JZP458 is administered IM at 25/25/50 mg/m2 MWF, 92.1% (95% CI, 90.9%-93.3%) of patients were expected to achieve the last 72-hour NSAA levels ≥0.1 IU/mL and 93.8% (95% CI, 92.7%-94.9%) of patients were expected to achieve the last 48-hour NSAA levels ≥0.1 IU/mL. **Asparagine depletion** ❖ Depletion of plasma asparagine was observed after IM JZP458 administration for all patients in all dosing cohorts. In course 1, mean pre-dose (baseline) L-asparagine concentrations ranged from 7.59-11.32 µg/mL for all dose levels and schedules, consistent with literature-reported values. ❖ For all cohorts following IM JZP458 administration, mean plasma asparagine levels rapidly declined from pre-dose levels to levels below or near the assay lower limit of quantitation (0.025 µg/mL); reduced plasma levels lasted throughout the treatment duration of course 1 up to pre-dose 6, when the last sample was collected. ❖ Plasma asparagine levels over time were similar across all 3 dosing schedules (i.e., MWF vs WFM vs. FMW).	**TRAEs:** n=124/167 (74.3%) **TRAEs grade 3 and 4**: n=86/167 (51.5%) **Discontinuation due to TRAEs**: n=21/167 (12.6%) **Treatment-emergent AEs that led to death[6]:** sepsis (cohort 1a, n = 1), aspiration pneumonia (cohort 1b, n = 1), multiorgan failure (cohort 1b, n = 1) **Allergic reactions related to JZP458**: n=16/167 (9.6%); including 3 (1.8%) with anaphylactic reaction **Treatment-related AEs** of hepatotoxicity, predominately elevation of liver enzymes, increased bilirubin, and/or ammonia of any grade; n=33/167 (19.8%) **Treatment-related hypertriglyceridemia**: n=12/167 (7.2%) **Grade 4 hypertriglyceridemia (deemed related to JZP458**): n=1/167 (3.0%) in cohort 1a and n=1/167 (2.0%) in cohort 1c.

[5] All patients in part A received pegaspargase before entering the study.
[6] None of which was deemed to be related to JZP458 treatment.

❖ Four patients had transient low-level increases in plasma asparagine (cohort 1a: 3 patients; and cohort 1b: 1 patient).	

Patient-reported outcomes

In JZP458 trial, patient-reported outcomes were not evaluated.

ESMO-MCBS for Haematological Malignancies [9]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	The ESMO-MCBS for Haematological Malignancies was not applicable because the primary endpoint "proportion of patients with the last 72-hour NSAA level ≥0.1 IU/mL" could not be assessed.										

Risk of bias - study level (case series) [10]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial[7]	yes	yes	yes	no[8]
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	unclear	unclear[9]	yes	yes	yes	yes

Overall risk of bias: moderate

Ongoing trials [11]

NCT number/trial name	Description	Estimated study completion date
NCT04526795	Phase Ib study of fludarabine, cytarabine (Ara-C) and pegylated Erwinase (pegcrisantaspase) in patients with relapsed or refractory leukaemia	12/2024

Available assessments

- ❖ In May and July 2023, CADTH published a reimbursement recommendation [12] and a reimbursement review [13] for "Crisantaspase recombinant (Rylaze®), respectively.
- ❖ No further assessments were identified.

Other aspects and conclusions

[7] Baseline characteristics were partially heterogenous.
[8] The trial was designed as an open-label study.
[9] At the data cutoff date for the results presented herein, some patients had not completed treatment.

- In July 2023, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Enrylaze® as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL and LBL in adult and paediatric patients (1 month and older) who developed hypersensitivity or silent inactivation to E. coli-derived asparaginase. In June 2021, the **FDA approved** asparaginase Erwinia chrysanthemi (recombinant)-rywn) (Rylaze®) as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL and LBL in adult and paediatric patients 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase.
- **AALL1931, an open-label, multicentre phase 2/3 study** investigated the efficacy and safety of JZP458 in paediatric or adult patients with newly diagnosed ALL/LBL if they developed a grade ≥3 allergic reaction to a pegylated E coli–derived asparaginase or silent inactivation. Patients were excluded if they had previously received native Erwinia-derived asparaginase or JZP458, had relapsed ALL/LBL, or a history of grade ≥3 pancreatitis.
- The **primary efficacy end point** of AALL1931 was the **proportion of patients with the last 72-hour NSAA level ≥0.1 IU/mL**. Following the first treatment course of JZP458, the proportion of patients who achieved NSAA levels ≥0.1 IU/mL at 72 hours was 64% (95% CI, 47%-82%) in cohort 1a, 91% (95%CI, 84%-97%) in cohort 1b, and 90% (95% CI, 81%-98%) in cohort 1c.
- Patient-reported outcomes were **not evaluated** in AALL1931.
- The **ESMO-MCBS** for Haematological Malignancies was **not applicable** because primary endpoint could not be assessed.
- The overall **risk of bias** was considered as **moderate**; it was **increased** by the open-label-design of the study, the partially heterogenous baseline characteristics and the fact that not all patients had completed treatment at data cutoff.
- Since no ongoing phase 3 trials were identified, **final analysis** of AALL1931 is required urgently. Furthermore, **patient-reported and long-term data are needed** to determine the role of Enrylaze® in this patient population.

First published: 08/2023
Last updated: 11/2023

Abbreviations: AE=adverse event, AJ=adjustment, ALL=acute lymphoblastic leukaemia, BMI=body mass index, BSA=body surface area, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, IM=intramuscular, Int.=intention, IV=intravenous, IQR=interquartile range, LBL=lymphoblastic lymphoma, MG=median gain, MWF=Monday/Wednesday/Friday, n=number of patients, NA=not available, NSAA=nadir serum asparaginase activity, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PK=pharmacokinetic, PM=preliminary grade, PopPK=population PK, QoL=quality of life, SAA=serum asparaginase activity, SAE=serious adverse event, ST=standard treatment, TRAE=treatment-related adverse event, ULN=upper limit of normal

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