Assessing the stability of Sandoz rituximab biosimilar after exposure to out-of-fridge conditions for 21 days

3PC-017

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Background and Importance

- Rituximab (RTX) is widely used in the treatment of several B-cell–derived haematological malignancies and non-oncology indications such as autoimmune diseases[1-5]
- Sandoz biosimilar of RTX (SDZ-RTX), Rixathon® or Riximyo®, is available as a concentrate solution for infusion as a single-dose vial[6]
- For any short-term temperature excursion outside the intended storage conditions, it is recommended to discard SDZ-RTX unless the excursion is permitted according to the provided patient leaflet
- There is a limited evidence on the effect of short-term temperature excursions on the quality of an unopened SDZ-RTX vial stored in the original outer box at caregiver level

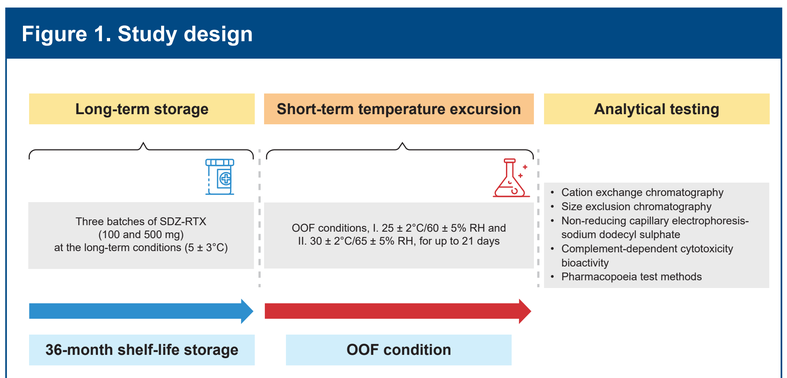
Aim and Objectives

- The study evaluated the extended physicochemical and biological stability of SDZ-RTX after exposure to out-of-fridge (OOF) conditions

Materials and Methods

- The OOF stability study was performed with three SDZ-RTX batches of 39–43 months age: one batch of 100 mg (10-mL vials) and two batches of 500 mg (50-mL vials)
- The study was designed to simulate temperature excursion outside the intended storage conditions of 2-8°C, with a duration of up to 21 days. The OOF study was performed at OOF condition I, 25 ± 2°C/60 ± 5% RH (climatic zone II) and OOF condition II, 30 ± 2°C/65 ± 5% RH (climatic zone IVa) (**Figure 1**)
- SDZ-RTX samples with the OOF duration of 21, 14 and 7 days were transferred from the intended conditions (2-8°C) into stability chambers of OOF conditions I or II on Day 0, 7 and 14, respectively

Figure 1. Study design



OOF, out-of-fridge; RH, relative humidity; SDZ-RTX, Sandoz rituximab

- The study also comprised SDZ-RTX reference sample, which was not exposed to the OOF conditions, based on which the effect of temperature excursion was evaluated
- On Day 21, all samples including reference samples were pulled from stability changes and subjected to analyses, thus, allowing direct head-to-head comparison and reducing potential variability of the analytical method
- Identity was assessed with cation exchange chromatography (CEX) and liquid chromatography-ultraviolet (LC-UV) peptide mapping
- Purity was assessed using CEX, size exclusion chromatography (SEC), and non-reducing capillary electrophoresis-sodium dodecyl sulphate (nrCE-SDS)
- Complement-dependent cytotoxicity (CDC)-bioactivity was utilized to assess potency
- Pharmacopoeia test methods were utilized to assess clarity, presence of visible and subvisible particles, container appearance, degree of coloration, pH, osmolality, extractable volume. Microbiological parameters assessed were sterility and bacterial endotoxins
- Integrity of container was evaluated with the container closure integrity testing
- Protein content was assessed with the ultraviolet (UV)/visible absorbance spectrometry

Results

- Slight changes in purity of SDZ-RTX, assessed with CEX, SEC and nrCE-SDS methods after exposure to OOF conditions I and II were noted (**Table 1**)

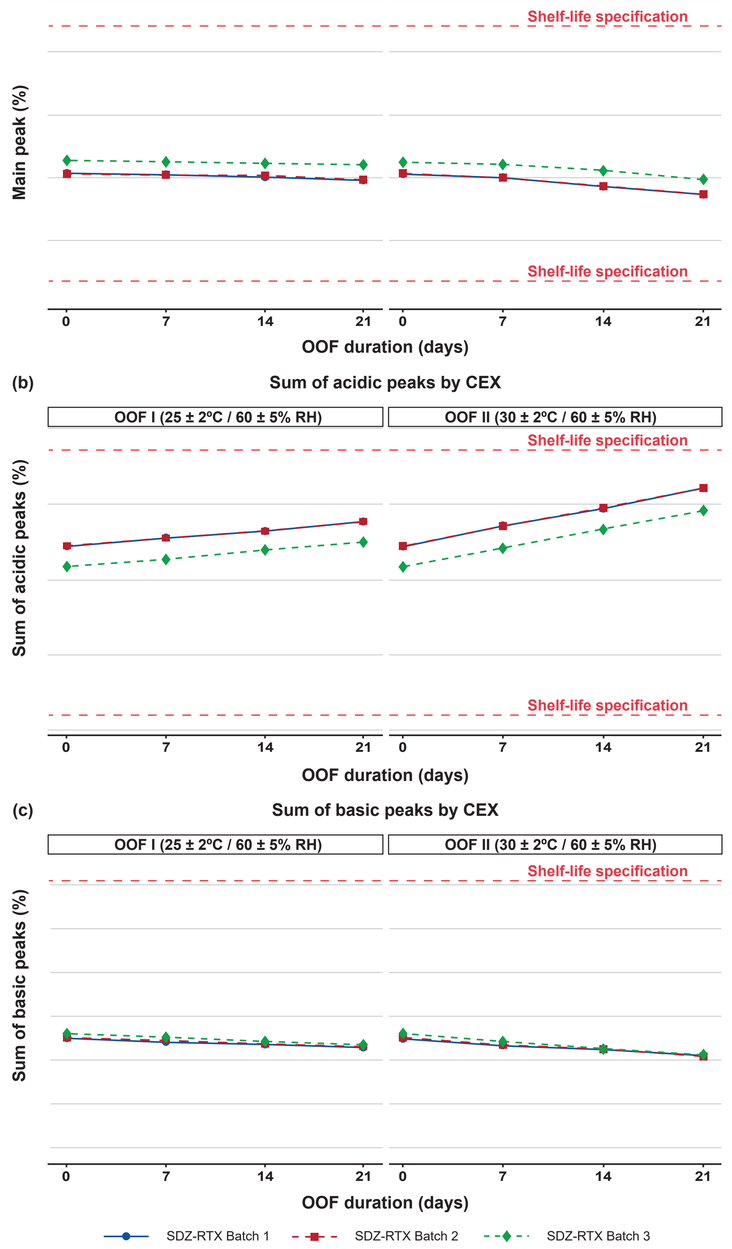
Table 1. Changes in SDZ-RTX after 21 days of OOF study

OOF duration	Δ after 21 days at 25 ± 2°C/60 ± 5% RH			Δ after 21 days at 30 ± 2°C/65 ± 5% RH		
	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
Purity by cation exchange chromatography						
Main peak (0K)	−0.5%	−0.6%	− 0.2%	−0.8%	−0.8%	−0.4%
SAP	+1.7%	+1.6%	+ 1.7%	+3.9%	+3.8%	+3.8%
SBP	−1.1%	−1.0%	−1.3%	−2.1%	−2.1%	−2.4%
Purity by size exclusion chromatography						
Purity	−0.1%	−0.2%	−0.2%	−0.4%	−0.4%	−0.4%
Sum of HMWs	0.0%	+0.1%	0.0%	+0.1%	+0.1%	0.0%
Purity by non-reducing capillary electrophoresis-sodium dodecyl sulfate						
Purity	−0.3%	−0.7%	−0.5%	− 0.9%	−0.7%	−0.5%
Potency						
CDC-bioactivity	−2%	+3%	−7%	+1%	−2%	−21%

CDC, complement-dependent lysis; HMW, high molecular weight; OOF, out-of-fridge; SAP, sum of acidic peaks; SBP, sum of basic peaks

- The analysis of SDZ-RTX purity with CEX revealed decrease in percentage of the main peak (**Figure 2a**), contaminant change in percentage of sum of acidic peaks (**increase, see Figure 2b**) and sum of basic peaks (**decrease, see Figure 2c**) was observed in all three SDZ-RTX batches after 21 days of OOF study

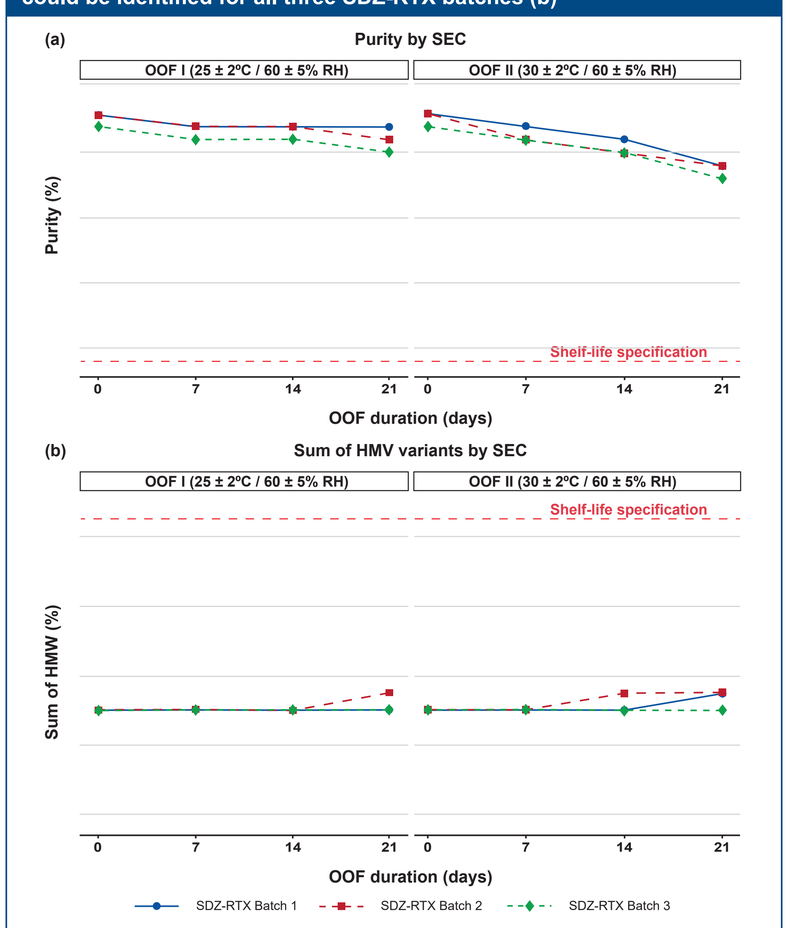
Figure 2. Throughout 21 days of storage at 25 ± 2°C/60 ± 5% RH and 30 ± 2°C/65 ± 5% RH, decrease in the main peak (a), increase in the sum of acidic peaks (b), and decrease in the sum of basic peaks (c) was observed for all three SDZ-RTX batches



CEX, Cation Exchange Chromatography; OOF, out-of-fridge; RH, relative humidity; SDZ-RTX, Sandoz rituximab

- The analysis of SDZ-RTX purity by SEC revealed decrease in purity of up to 0.4% (**Figure 3a**) after 21 days of the temperature excursion. For the sum of high molecular weight (HMW) variants, no clear common trend could be determined as the results fluctuated by maximally 0.1% (**Figure 3b**)

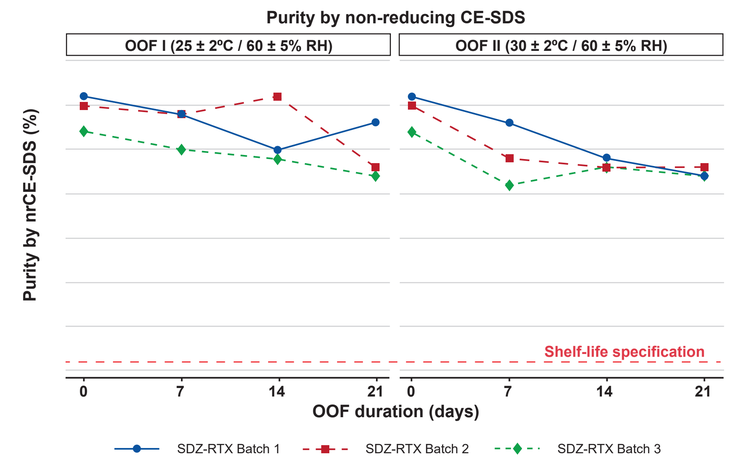
Figure 3. Throughout 21 days of storage at 25 ± 2°C/60 ± 5% RH and 30 ± 2°C/65 ± 5% RH, measurement of purity by SEC revealed slight decrease in purity (a). For the sum of HMWs, no clear common trend could be identified for all three SDZ-RTX batches (b)



HMV, high molecular weight; OOF, out-of-fridge; RH, relative humidity; SDZ-RTX, Sandoz rituximab; SEC, Size Exclusion Chromatography

- The analysis of SDZ-RTX purity by non-reducing CE-SDS revealed a decrease in purity of up to 0.9% (**Figure 4**), which complies with the shelf-life specification limits defined for SDZ-RTX

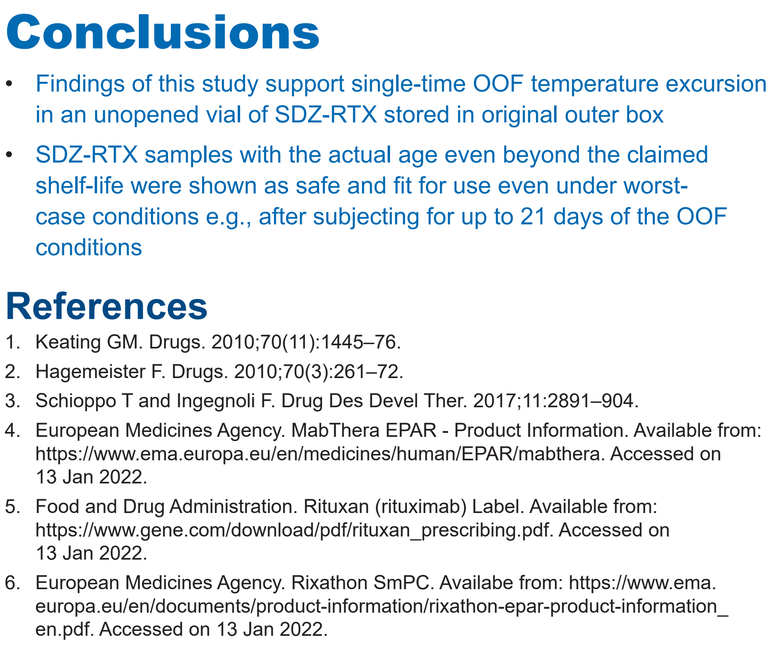
Figure 4. Assessment of purity by nrCE-SDS



OOF, out-of-fridge; RH, relative humidity; SDZ-RTX, Sandoz rituximab

- For potency, which was measured with CDC-bioactivity, no common trend in stability behaviour could be determined for all three tested SDZ-RTX batches. At OOF condition I (25 ± 2°C/60 ± 5% RH) changes within the range of method variability can be seen for all three tested batches. At OOF condition II (30 ± 2°C/60 ± 5% RH), decrease in potency was observed only in one of the three tested SDZ-RTX batches; however, variation in data was observed in other two SDZ-RTX batches (**Figure 5**)

Figure 5. Potency of SDZ-RTX measured by CDC-bioactivity of the temperature excursion study during 21 days of storage at 25 ± 2°C/60 ± 5% RH and 30 ± 2°C/65 ± 5% RH



OOF, out-of-fridge; RH, relative humidity; SDZ-RTX, Sandoz rituximab

- No notable changes were observed across all batches in clarity (6 NTU [nephelometric turbidity unit] in all batches), visible and subvisible particles, container appearance, degree of coloration, pH, osmolality, extractable volume, and container closure integrity testing, protein content by UV spectrometry
- For microbiological tests, no notable changes were observed. All three batches meet the specification limits

Conclusions

- Findings of this study support single-time OOF temperature excursion in an unopened vial of SDZ-RTX stored in original outer box
- SDZ-RTX samples with the actual age even beyond the claimed shelf-life were shown as safe and fit for use even under worst-case conditions e.g., after subjecting for up to 21 days of the OOF conditions

References

1. Keating GM. Drugs. 2010;70(11):1445–76.
2. Hagemeister F. Drugs. 2010;70(3):261–72.
3. Schioppo T and Ingegnoli F. Drug Des Devel Ther. 2017;11:2891–904.
4. European Medicines Agency. MabThera EPAR - Product Information. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/mabthera. Accessed on 13 Jan 2022.
5. Food and Drug Administration. Rituxan (rituximab) Label. Available from: https://www.gene.com/download/pdf/rituxan_prescribing.pdf. Accessed on 13 Jan 2022.
6. European Medicines Agency. Rixathon SmPC. Availabe from: https://www.ema.europa.eu/en/documents/product-information/rixathon-epar-product-information_en.pdf. Accessed on 13 Jan 2022.

Disclosures

All authors are employees of Novartis. All authors participated in the development of the poster and approved the final poster for presentation.

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