

Evaluation of In-Use Physicochemical Stability of Diluted Isatuximab (ISA)

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I. Introduction

📌 Clinical Context

Isatuximab (SARCLISA®): chimeric IgG1 monoclonal antibody targeting CD38

expressed on normal and tumor hematopoietic cells

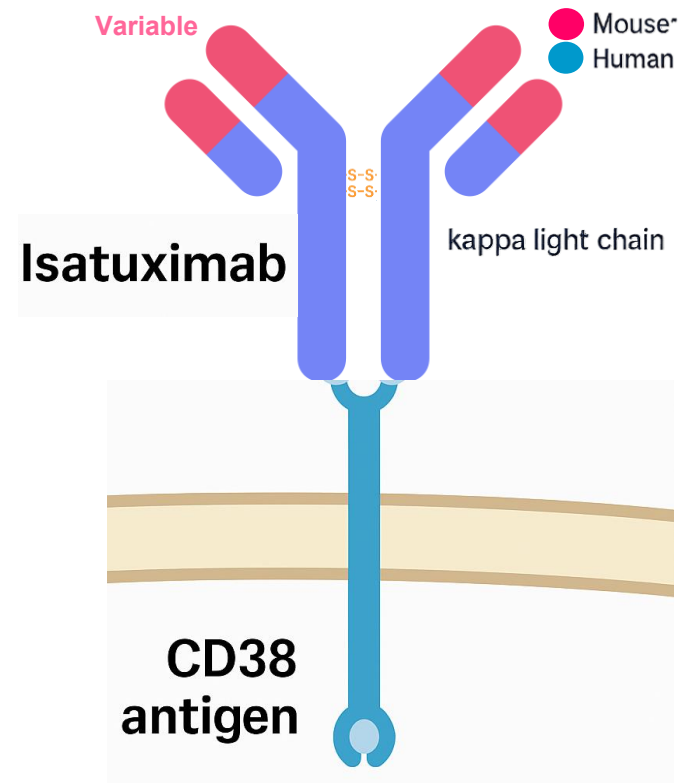
Indication: multiple myeloma (from 2nd line)

💬 Current Issue

Post-dilution stability limited to 48h at 2 – 8 °C and 8h at 15 – 25 °C (as per SmPC).

Hospital pharmacy constraints:

- No anticipation of preparations beyond 24h.
- No possibility of reallocation if the patient cancels (e.g. Pitié Salpêtrière: economic losses of €32,872 in 2024; projected to exceed €40,000 in 2025).
- No possibility to prepare standard doses in advance.
- Environmental impact (antibody recycling cost).





Study objectives




Evaluate the physicochemical stability of Isatuximab for 28 days at 2 - 8 °C



Optimize pharmaceutical management (workflow, costs, ecology)



Explore the possibility of extending in-use duration



II. Materials and Methods



Materials:

- Drug: Isatuximab (SARCLISA®) 20 mg/mL (~150 kDa)
- NaCl 0.9% (Fresenius)

Stress testing (ICH, Q1A (R2))

Conditions	Dilution solvent	Analysis
Temperature 60 °C	NaCl 0.9%	J0, J1, J7
Freeze/thaw (3 cycles 24h-80 °C)	NaCl 0.9%	After 3rd cycle
NaOH 0.1N ; HCl 0.1N	NaCl 0.9%	J0, J1, J7
Photolysis	NaCl 0.9%	J0, J1, J7
Agitation (Vortex, 1000 rpm)	NaCl 0.9%	15, 30, 60, 90 min
Oxidizing environment	H ₂ O ₂ 0.1%	1h, 6h, 12h, 24h, J7

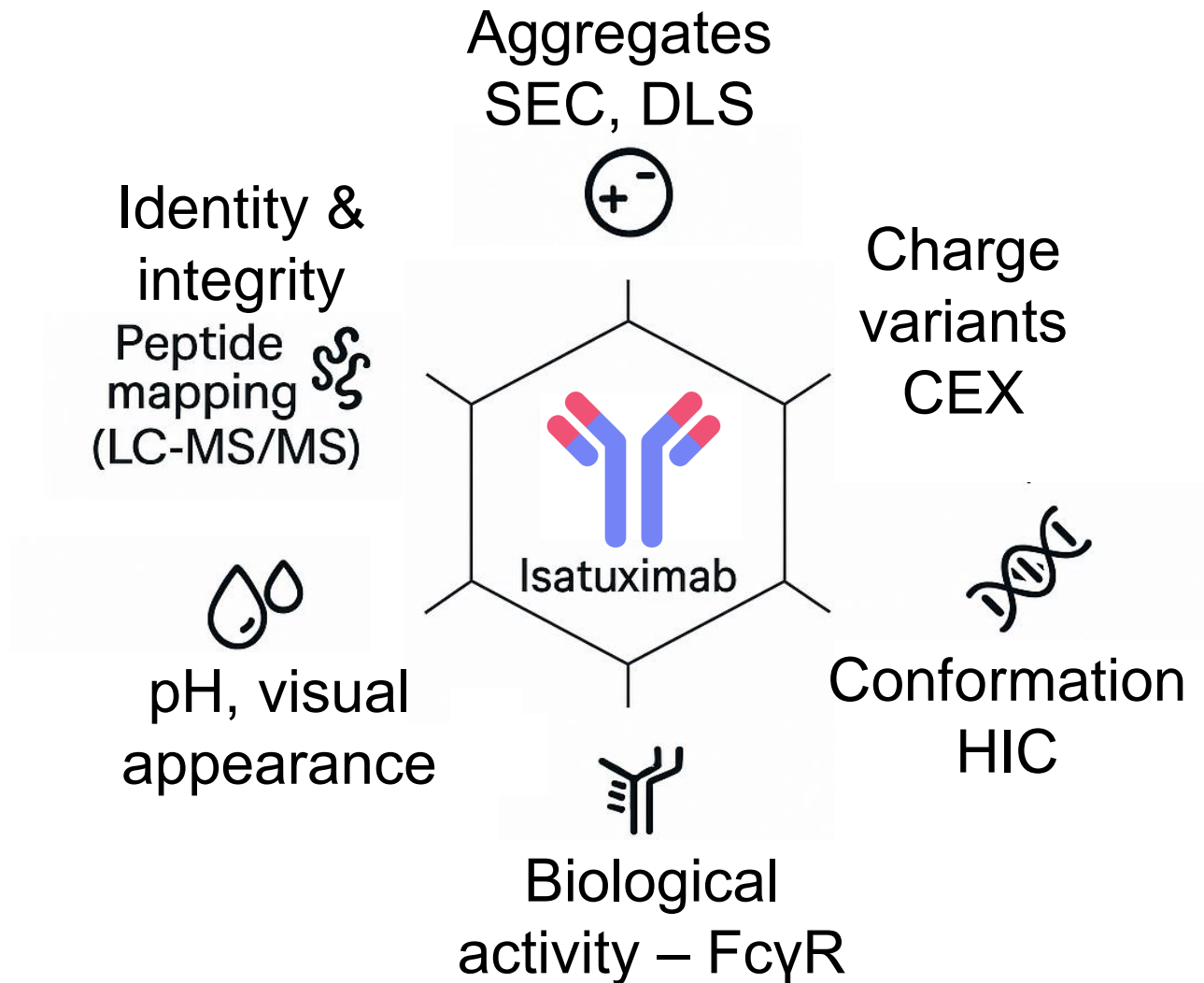
Long term stability

Concentration (mg/mL)	No. of bags (3 per batch)	Storage (°C)
1	6 (2 batches)	2 – 8 
3	6 (2 batches)	2 – 8 

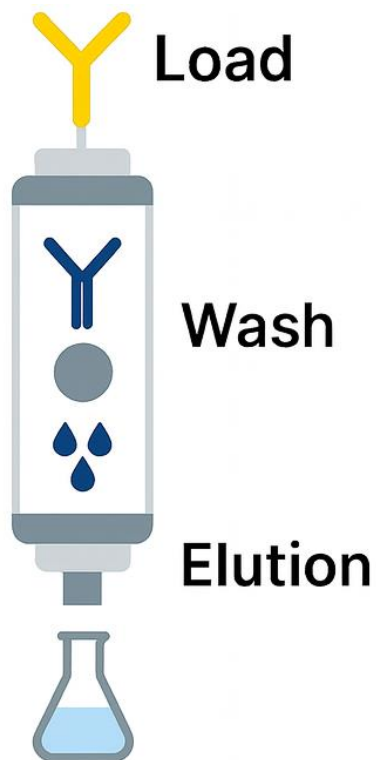


II. Materials and Methods

Qualitative Methods – Analytical Techniques



II. Materials and Methods



Quantitative method Protein A Affinity chromatography

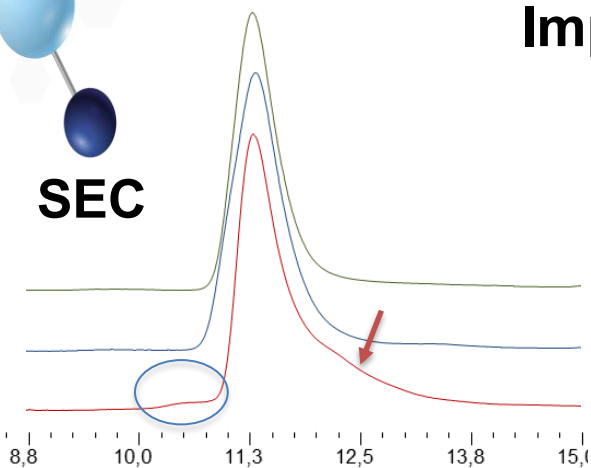
- ✓ **Validation**
 - ✓ Specificity
 - ✓ Linearity
 - ✓ Precision / Repeatability
 - ✓ Accuracy
 - ✓ Robustness
 - ✓ LOD / LOQ

ICH Q2(R1) validation – guaranteeing accurate, robust, and reliable quantification of isatuximab.

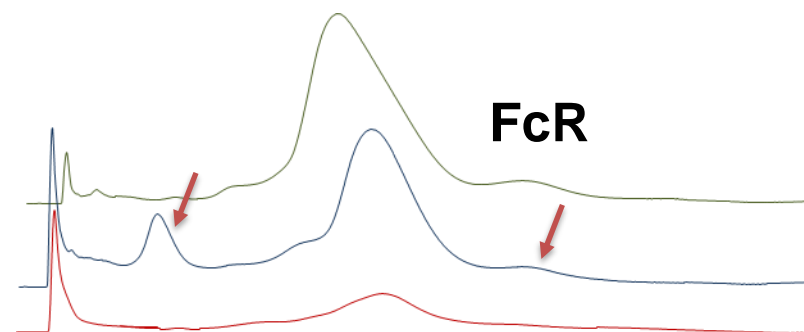
III. Results

Impact of Stress Conditions

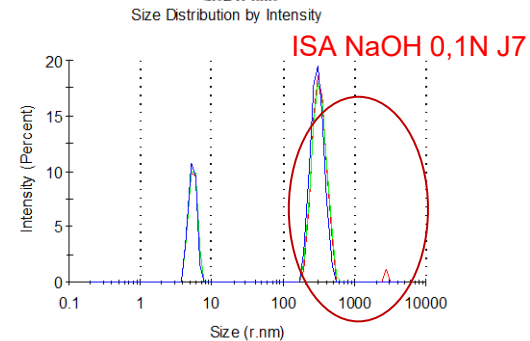
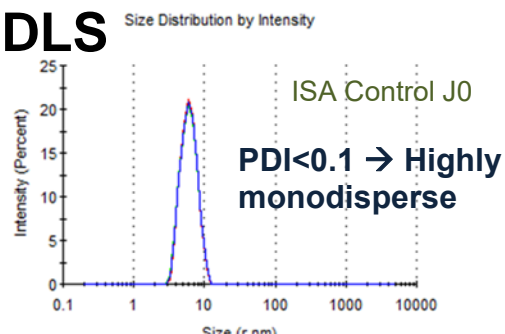
SEC



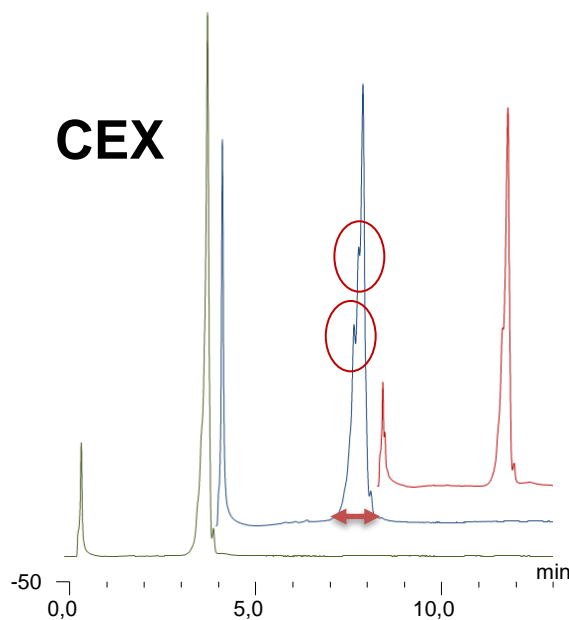
FcR



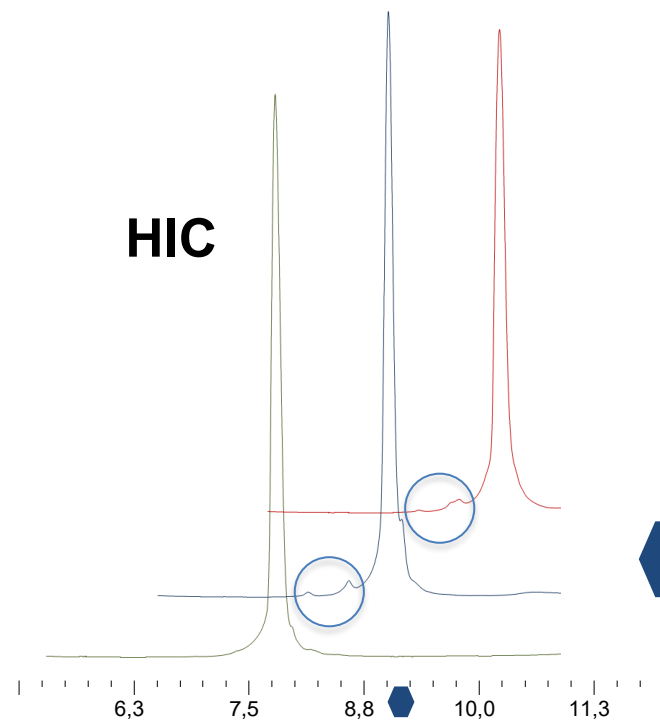
DLS



CEX



HIC



III. Results



Qualitative Methods: Illustrative Comparison of J0 vs J28 Results

Visual inspection: no loss of transparency or visible color changes ✓

pH: remained stable, with no significant variation across all samples ✓

Peptide Mapping by Tryptic Digestion and Mass Spectrometry ✓

- Tryptic peptide mapping confirmed >90% sequence coverage

ISA heavy chain (450 AA)

QVQLVQSGAEVAKPGTSVKLSCKASGYTFTDYWMQWVKQRPGQGLEWIGTIYPGDDGTGYAQKFQGKATLTAD
KSSKTVYMHLSLASEDSAVYYCARGDYYGSNSLDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK
DYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

ISA light chain (214 AA)

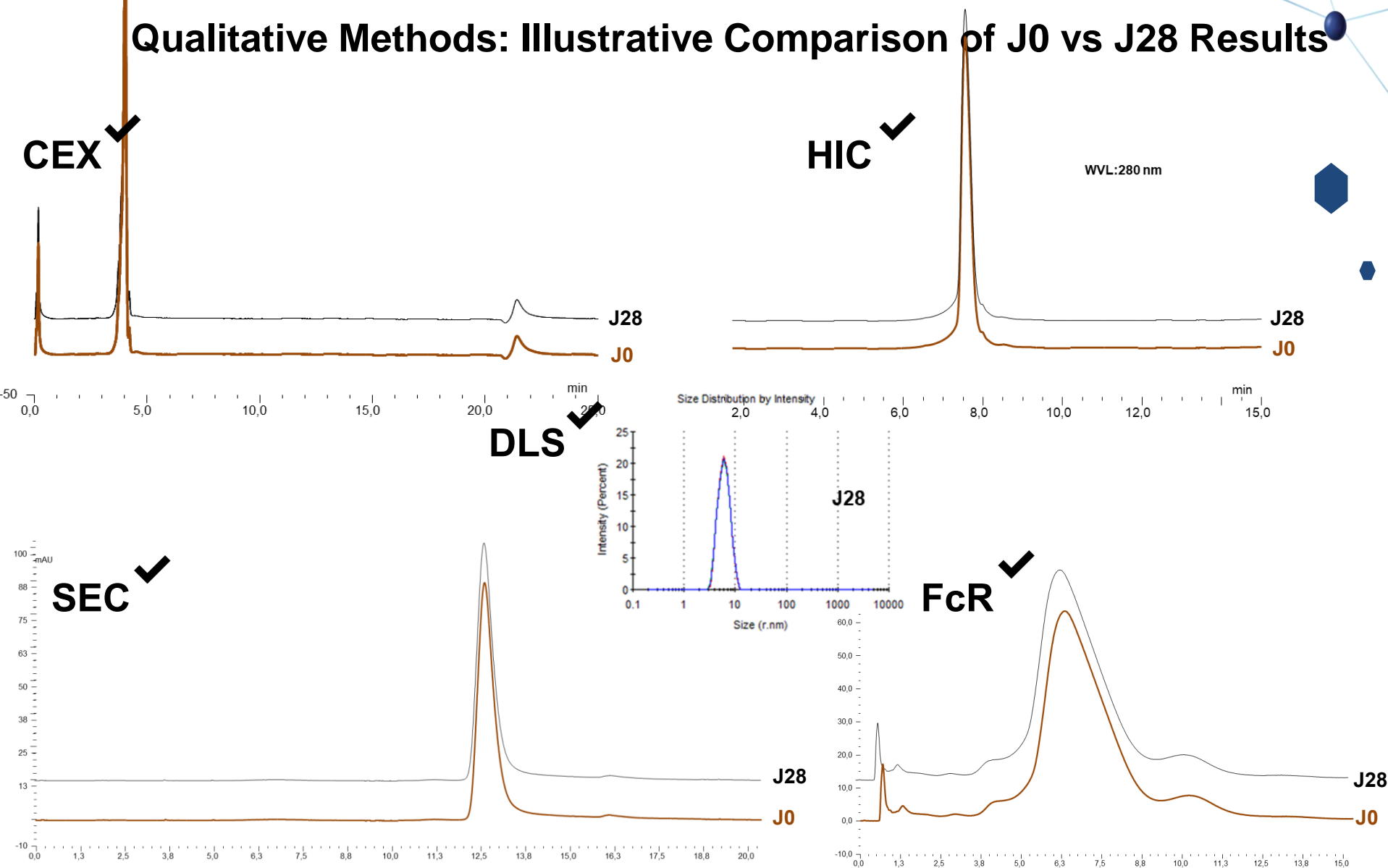
DIVMTQSHLSMSTSLGDPVSITCKASQDVSTVVAWYQQKPGQSPRRLIYSASYRYIGVPDRFTGSGAGTDFTFTISS
VQAEDLAVYYCQGHYSPPYTFGGGTKLEIKRTVAAPSVEFIPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL
QSGNSQESVTEQDSKDSYSLSSLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

- No significant structural modifications between Day 0 and Day 28
- No additional degradation products observed



III. Results

Qualitative Methods: Illustrative Comparison of J0 vs J28 Results



Qualitative analytical approaches collectively confirmed the preservation of antibody stability over the 28-day study period.

III. Results

Quantitative Method – Protein A Affinity Chromatography

Method validation ✓

Specificity

Protein A Affinity

Linearity

- $y = 10.085x + 0.5532$
- $R^2 = 0.9992$

Repeatability (Precision)

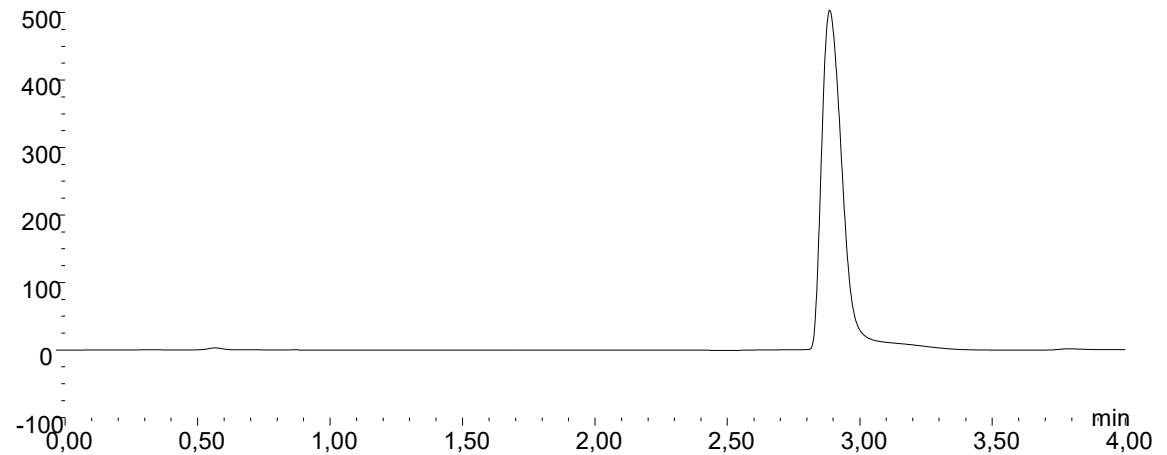
- Repeatability CV = 1.32% (<2%)
- Intermediate Precision = 2.06% (<5%)

Accuracy

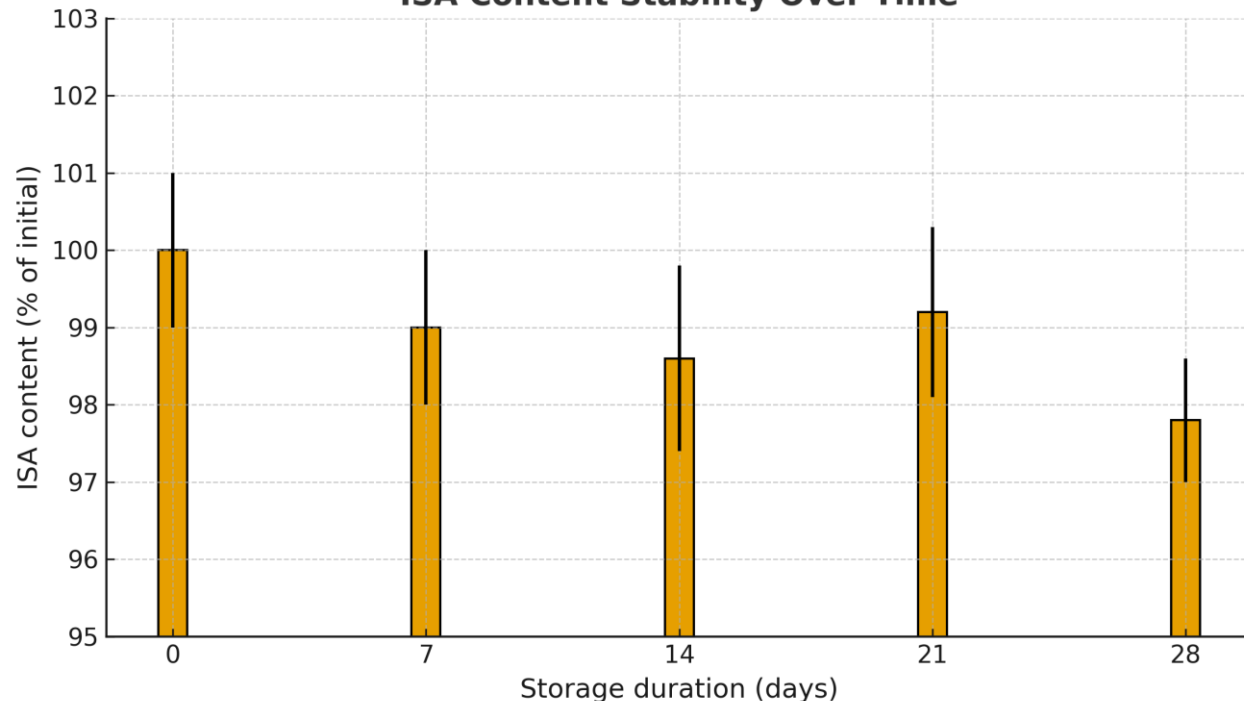
- Recovery Rate = 99.79% (98–101%)

Long-term stability ✓

- Stable for 28 Days (<5% variation)

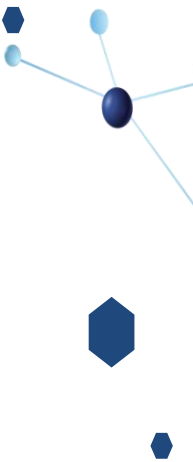


ISA Content Stability Over Time



Antibody stability confirmed by quantitative method (J0 vs J28) ✓

IV. Conclusion - Discussion



Stability of Isatuximab: Key Findings and Implications



Stress conditions

- Degradation observed under stress conditions: acidic, basic, oxidative, light, and freeze–thaw cycles
- No significant impact from agitation



Extended stability

- Excellent physicochemical stability maintained over **28 days at 2 – 8°C**
- Clear improvement compared with the **48 h limit in the SmPC**

Implications :



For patients



Healthcare institutions



Environment



A cluster of blue geometric shapes in the top right corner, including a central dark blue circle connected by thin lines to several smaller light blue circles, and a few isolated dark blue hexagons.

Thanks!

Do you have any questions?

A small, isolated dark blue hexagon in the bottom left corner.