Adverse Event Safety Narrative

Protocol Number: XYZ-101-RA-02
Subject Identifier: 101-08-204
Adverse Event: Grade 2 Acute Infusion-Related Hypersensitivity Reaction
Causality Assessment: Suspected (Possibly Related)

1. Patient Background and Baseline Characteristics

Subject 101-08-204 was a 54-year-old female who was enrolled in the Phase II multi-center trial evaluating the safety, tolerability, and efficacy of XYZ-101 in moderate-to-severe rheumatoid arthritis.

- **Medical History:** Her relevant background medical history included a 7-year history of erosive, seropositive rheumatoid arthritis, secondary osteoarthritis of the bilateral knees, mild seasonal allergic rhinitis, and generalized anxiety disorder.
- **Concomitant Medications:** At the time of the event, her stable concomitant maintenance medications included Methotrexate (20 mg orally, weekly), Folic Acid (5 mg orally, daily), and Loratadine (10 mg orally, daily as needed for allergic rhinitis). She had no documented history of drug or food hypersensitivity.

2. Chronological Timeline of the Adverse Event

Treatment Administration

On 14-Apr-2026 (Study Day 1), the subject successfully completed her first intravenous (IV) infusion of double-blind investigational product (IP) without incident. On 12-May-2026 (Study Day 29), she returned to the investigational site for her second scheduled protocol administration (Dose 2). The IV infusion of XYZ-101/Placebo commenced at exactly 10:15 AM.

Onset of Symptoms

At 10:45 AM, approximately 30 minutes into the planned 60-minute infusion window, the subject reported acute generalized pruritus, a warm sensation in her face, and localized itching around the IV catheter site in her left forearm.

Clinical Examination & Vitals

The Study Coordinator immediately checked the subject's vital signs and alerted the Principal Investigator (PI). Physical examination revealed confluent, raised erythematous wheels (urticaria) localized to the left upper extremity and upper chest, along with visible facial flushing. There was no evidence of angioedema (no swelling of the lips, tongue, or periorbital tissue), and no signs of respiratory distress or stridor.

Vital signs remained stable and did not indicate hemodynamic compromise or anaphylaxis:

Time	Event Milestone	Blood Pressure	Heart Rate	Oxygen Saturation	Temp
10:00 AM	Pre-infusion Baseline	122/78 mmHg	74 bpm	99% (Room Air)	36.6°C
10:45 AM	**Event Onset**	128/82 mmHg	88 bpm	98% (Room Air)	36.8°C
11:15 AM	Post-Treatment Review	120/74 mmHg	78 bpm	99% (Room Air)	36.5°C

3. Therapeutic Interventions and Clinical Outcome

Action Taken with Investigational Product

The IV infusion was **temporarily interrupted** immediately at 10:45 AM upon symptom recognition. A total of approximately 75 mL of the planned 150 mL infusion volume had been administered to the subject prior to the halt.

Medical Management

The PI graded the acute hypersensitivity reaction as **Grade 2** (moderate, localized systemic intervention indicated) according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The subject was immediately treated at the bedside with a single oral dose of the H1-antihistamine **Diphenhydramine (50 mg)**.

Resolution

The subject was placed under continuous visual surveillance. Within 45 minutes of antihistamine administration, the facial flushing began to recede, and the localized urticaria significantly decreased in intensity. By 12:45 PM (exactly 2 hours post-event onset), all clinical symptoms had completely resolved.

Because the subject was completely asymptomatic and hemodynamically stable, the PI determined that the remaining 75 mL of the infusion could be cautiously re-initiated at a reduced rate (half-speed) under intense medical supervision. The remainder of Dose 2 was successfully completed at 2:00 PM without any secondary recurrence of systemic or localized symptoms. The subject was monitored at the clinic for an additional 2 hours and was discharged home in stable condition.

4. Investigator Causality and Protocol Impact

Causality Rationale

The Principal Investigator assessed the Grade 2 acute infusion-related hypersensitivity reaction as **possibly related** (suspected) to the investigational product. The clinical justification was based entirely on the strict temporal relationship between the initiation of the IV infusion and the rapid onset of classical Type I immediate hypersensitivity symptoms, which match the known risks associated with modern humanized monoclonal antibody infusions.

Ongoing Protocol Participation

The event did not meet any protocol-defined stopping or discontinuation criteria (Section 5.3), which require permanent withdrawal only for severe anaphylactic or Grade 3/4 hypersensitivity events. The subject remained enrolled in the study.

For her third and final scheduled protocol infusion at Week 8 (09-Jun-2026), the site implemented an enhanced safety monitoring plan, which included pre-medication with oral Cetirizine (10 mg) 1 hour prior to the visit and an extended post-infusion observation window of 4 hours. Dose 3 was completed with zero adverse symptoms.

5. Regulatory Conclusion

This isolated case represents a transient, non-serious, Grade 2 acute infusion-related hypersensitivity reaction that was quickly resolved with standard first-line medical therapy. This event does not constitute a new safety signal, is structurally consistent with the safety profile of biological immunotherapies, and does not alter the overall positive benefit-risk assessment of XYZ-101 for the treatment of moderate-to-severe rheumatoid arthritis.