

Pilot Phase II Study of Humanized Anti-CD22 Monoclonal Antibody, hLL2 (Epratuzumab), in Systemic Lupus Erythematosus Therapy

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→ Rationale / Objectives

- **B-cells Play Important Role in Pathogenesis of Autoimmune Disorders**
- **First Pilot Study of anti-CD22 MAb, hLL2 (*Epratuzumab*, Immunomedics, Inc.), in SLE**
- **Study Objectives:**
 - **Confirm Safety, Tolerance and Lack of Immunogenicity in SLE**
 - **Evaluate Early Evidence of Efficacy in SLE**
 - **Assess Pharmacokinetics and Pharmacodynamics**

→ Study Design

- Open-Label, Non-Randomized Study
- ~15 Pts
- Screening/Baseline Evaluations
- **360 mg/m² epratuzumab q 2 wks X 4 Doses**; All Pts Premedicated (antihistamine, acetaminophen)
- Post-Treatment (**after last infusion**) Evaluations 24 h, 4 wks, 12 wks, 6 month Follow-Up

→ **Efficacy**

BILAG

8 Organ-based Systems:

- **General** (fatigue, fever, anorexia, wt loss, etc.)
- **Mucocutaneous** (rash, alopecia, mucosal ulcers, etc.)
- **Neurologic** (headache, seizure, delirium, etc.)
- **Musculoskeletal** (arthritis, myalgia, etc.)
- **Cardiovascular/Respiratory** (rub, dyspnea, effusion, etc.)
- **Vasculitis** (Raynauds, thromboembolism)
- **Renal** (proteinurea, renal insufficiency, etc.)
- **Hematologic** (cytopenias, coagulopathy, etc.)

Each Individually Assessed for Activity: 0 – 9 Scale

Global Activity Scale Summed Scores (0 - 72)

→ Patient Population

- Males or Females \geq 18-years-old
- SLE by ACR Revised Criteria (\geq 4/11 criteria)
- SLE \geq 6 months
- Moderately Active Disease (6 –12 on BILAG Index)
- No Prior Rituximab/Other Anti-B-cell MAb Therapies
- Adequate Laboratories: Hematology (Hgb $>$ 8, WBC $>$ 2,000, Plts $>$ 50,000), Renal (Crea $<$ 2.5 mg/dL), and Liver (ALT, AST, Alk Phos $<$ 2 X ULN)
- Other Standard Safety Criteria

→ **Study Procedures**

- **SLE Activity: Clinical Signs, Symptoms, SLE Panel (Autoantibodies, C3, CRP, ESR, Other Labs), VAS (global assessment of disease activity, arthralgia, fatigue)**
- **Toxicities/Adverse Events (NCI CTC v 2.0)**
- **Vital Signs, Physical Examinations**
- **Routine Safety Labs (hematology, chemistry, UA)**
- **Serum Immunoglobulins**
- **Peripheral Blood B and T cells**
- **hLL2 Levels**
- **Human Anti-hLL2 Antibodies (HAHA)**

→ **Study Population**

- **14 Pts Enrolled and Treated**
- **13F / 1M, 22 – 52 years old**
- **Median Yrs Post Diagnosis: 10.1 (1.07-18.6)**
- **11 Pts Received 0- 4 Prior Therapies**
- **Most Frequent Presenting Criteria:**
 - **14/14: Antinuclear antibody, Photosensitivity**
 - **11/14: Immunologic disorder**
 - **10/14: Malar rash**
 - **8/14: Hematologic disorder**

→ Study Population (con't)

- **Disease Activity Levels at Entry**
 - BILAG Median Global Scores: 9 (range, 6 - 12)
 - No pts had A-level activity in any system
 - 13/14 pts had B-level activity in ≥ 1 systems:
typically mucocutaneous, vasculitis, or cardiovascular/respiratory/ no renal or CNS
- **Concomitant Medications at Entry**
 - Prednisolone, < 10 mg/day (N = 6)
 - Azothioprine, 50-200 mg/day (N = 6)
 - Methotrexate, 15-20 mg/day (N = 3)

→ **Safety**

Adverse Events (N=14)

Infusion Time: Median: 31.5 minutes (Range: 23 – 86 minutes)

No Infusion Reactions

Adverse Events Reported

- 1 Pt: **Sleepiness** at 1st Infusion. Attributed to IV antihistamine premedication. Pt received 2nd - 4th infusions without event.
- 1 Pt: **Herpes Zoster**. Developed after 2nd Infusion and discontinued therapy. Responded to antivirals.
- 1 Pt: **Otitis media**. Developed after 4th Infusion. Responded to antibiotics.

Study of Humanized LL2 (Epratuzumab) in SLE

→ Safety

Standard Hematology/Chemistry (N=14)

Parameter	Unchanged from Baseline	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hematology					
Hemoglobin	14	0	0	0	0
Platelets	14	0	0	0	0
WBC	14	0	0	0	0
Chemistry					
Creatinine	11	3	0	0	0
T. Bilirubin	14	0	0	0	0
Alk. Phos.	12	2	0	0	0
ALT	10	1	2 *	1 ‡	0
AST	10	3	1 *	0	0
GGT	12	0	2 *	0	0

* CTC Grade 1 At Baseline

‡ CTC Grade 2 At Baseline

Pharmacokinetics/Immunogenicity

- PK: Measurable serum epratuzumab levels achieved after treatment and 4 weeks later
- HAHA: No evidence of immunogenicity by ELISA assay sensitive to < 25 ng/ml

Time post 4th Infusion	Samples Analyzed	epratuzumab (ug/mL) Mean (range)	HAHA Increase from Baseline
24 hours	12	158 (49-350)	0
4 weeks	7	79 (31-137)	0
12 weeks	6	6.5 (<0.5 – 21)	0

B & T CELLS, IMMUNOGLOBULINS

- Consistent Decrease in B Cells After Treatment
- No Consistent Changes in T Cells, IgG, IgA, IgM

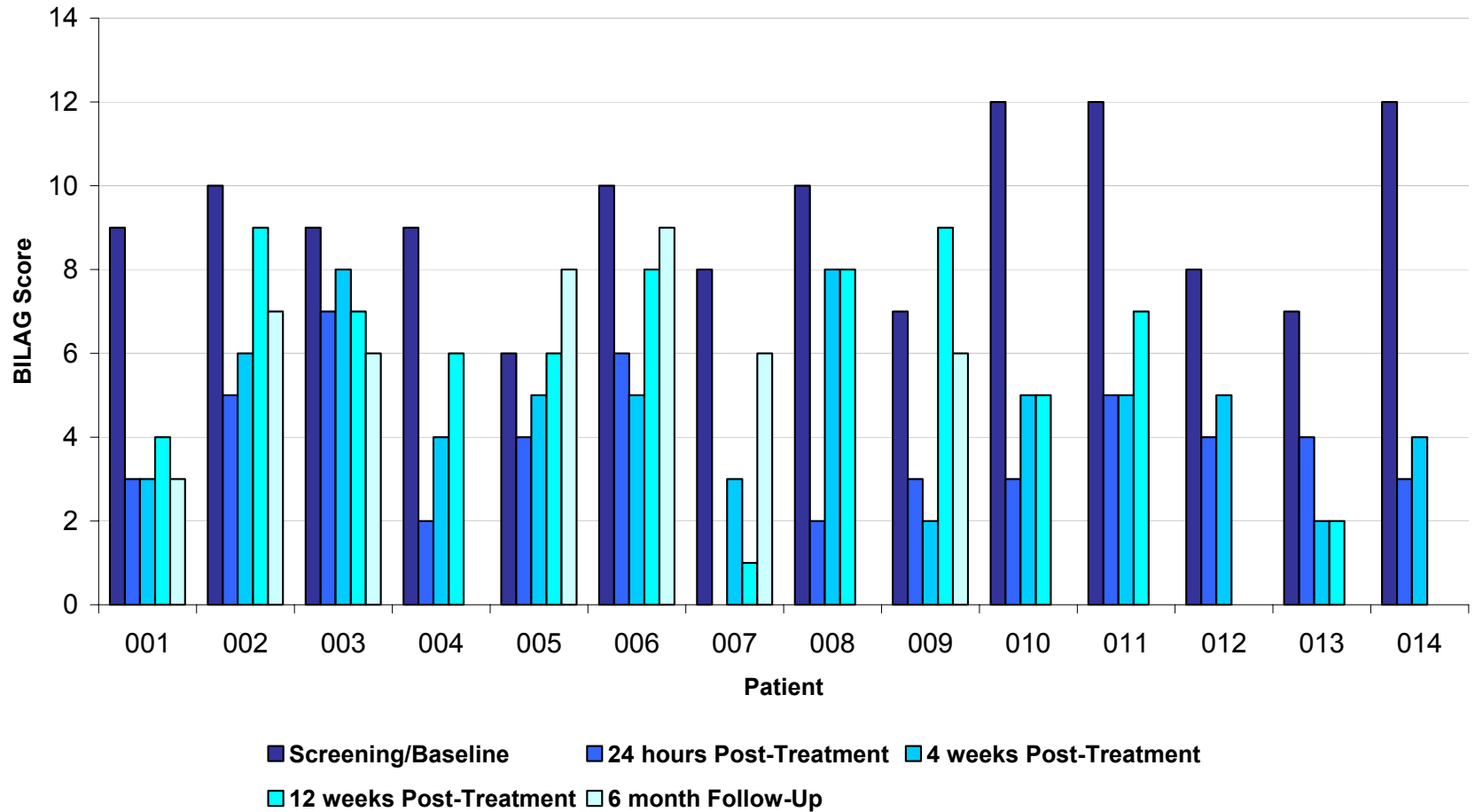
	Percent of Baseline (Mean +/- SD)*			
	24 hours post last infusion	4 weeks	12 weeks	6 months
B-cells	65% +/- 21%	59% +/- 38%	58% +/- 17%	40% +/- 15%
T-cells	116% +/- 73%	128% +/- 73%	97% +/- 45%	76% +/- 28%
IgG	102% +/- 8%	105% +/- 13%	108% +/- 16%	97% +/- 1%
IgA	104% +/- 11%	107% +/- 13%	104% +/- 15%	108% +/- 18%
IgM	86% +/- 16%	96% +/- 21%	88% +/- 13%	87% +/- 8%

*Lymphocytes, 4-8 samples/timepoint; Immunoglobulins, 5-10 samples/timepoint

Study of Humanized LL2 (Epratuzumab) in SLE

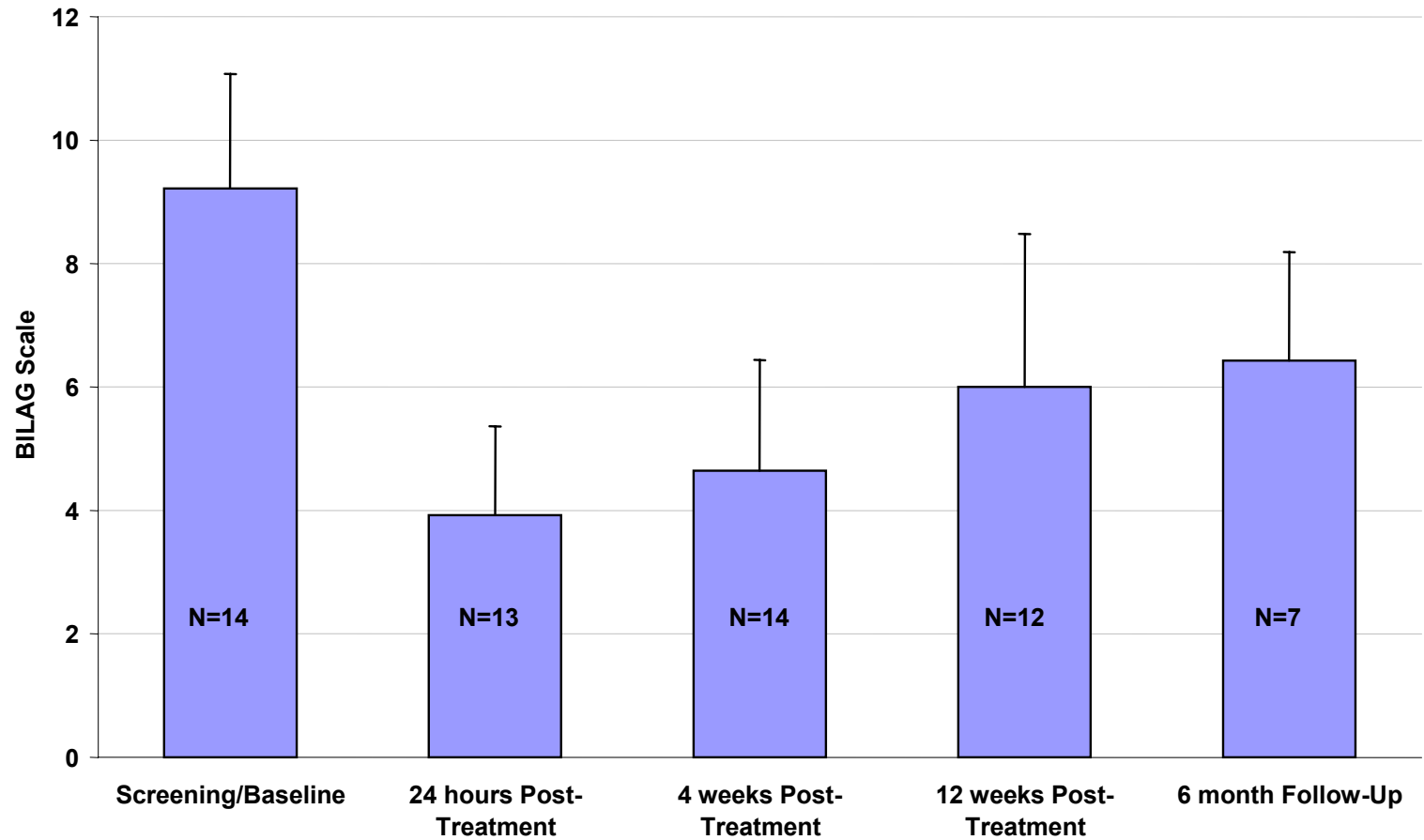
→ **Efficacy**

Patient Global BILAG Scores



Study of Humanized LL2 (Epratuzumab) in SLE

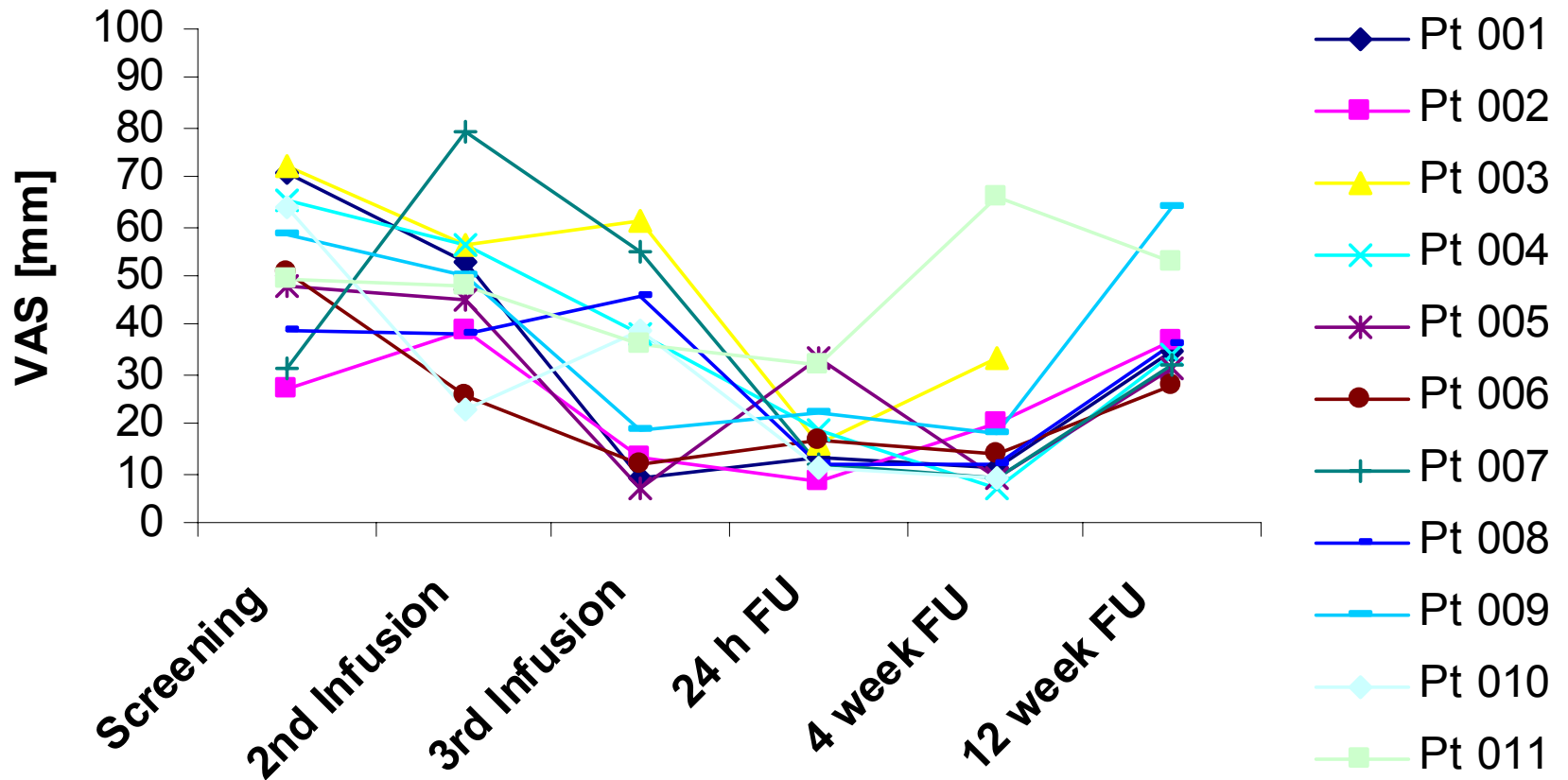
→ Interim Efficacy Mean BILAG Scores



Mean and Standard Deviation by Visit

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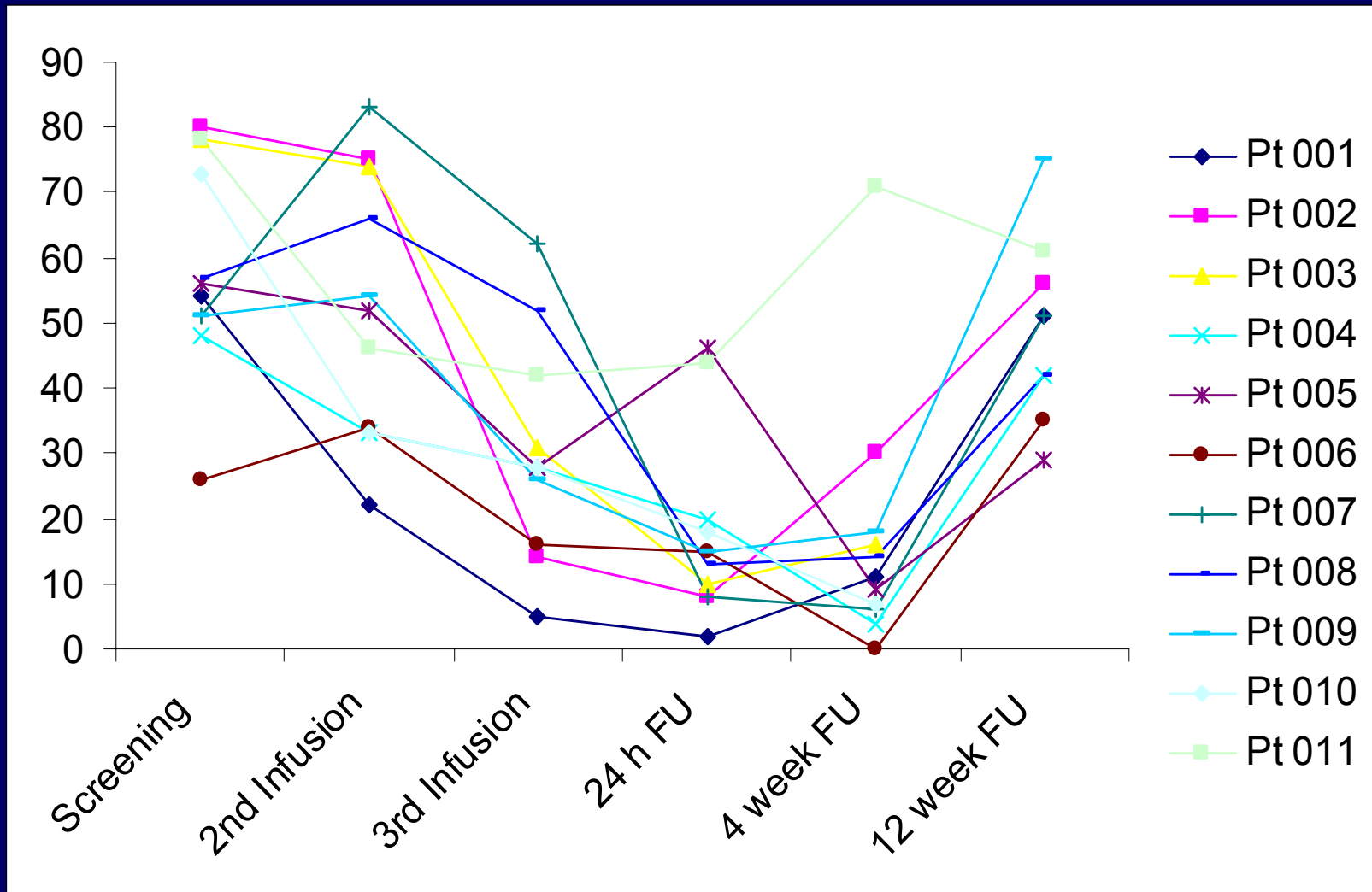
→ Interim Efficacy VAS: Pts. Global Assessment of Disease Activity



Study of Humanized LL2 (Epratuzumab) in SLE

→ Interim Efficacy

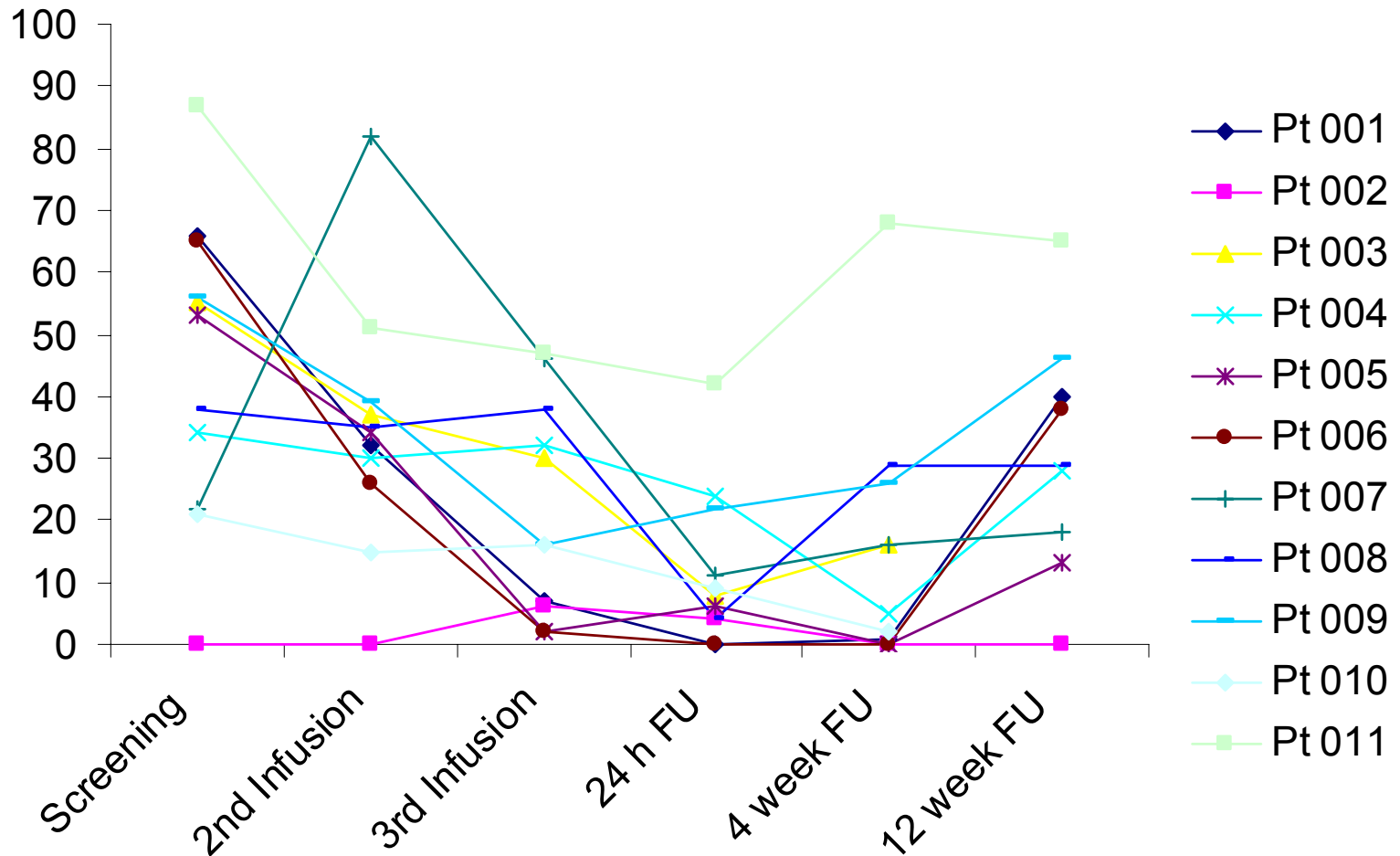
VAS: Fatigue



Study of Humanized LL2 (Epratuzumab) in SLE

→ Interim Efficacy

VAS: Arthralgia



SUMMARY

Epratuzumab (hLL2) Immunotherapy

- **Safe and well tolerated**
- **Symptomatic improvement in all pts**
- **Administered < 1 hr without significant infusion reactions**
- **Achieved consistent antibody serum levels, decreased B-cell levels**
- **No evidence of immunogenicity, T-cell or immunoglobulin alterations**