

Erythropoiesis Sustained 12 months by the EPODURE Biopump in Patients with Chronic Kidney Disease: Further Results of Phase I/II Proof of Concept Trial

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Anatole Besarab, Doron Schwartz, Ehud Shoshani, Andrew L. Pearlman,
Baruch Stern, Philip Ng, Allen R. Nissenson, and Michal Dranitzki Elhalel

Henry Ford Hospital, Detroit, MI, USA

Sourasky Medical Center, Tel Aviv, Israel

Medgenics Inc., Misgav, Israel

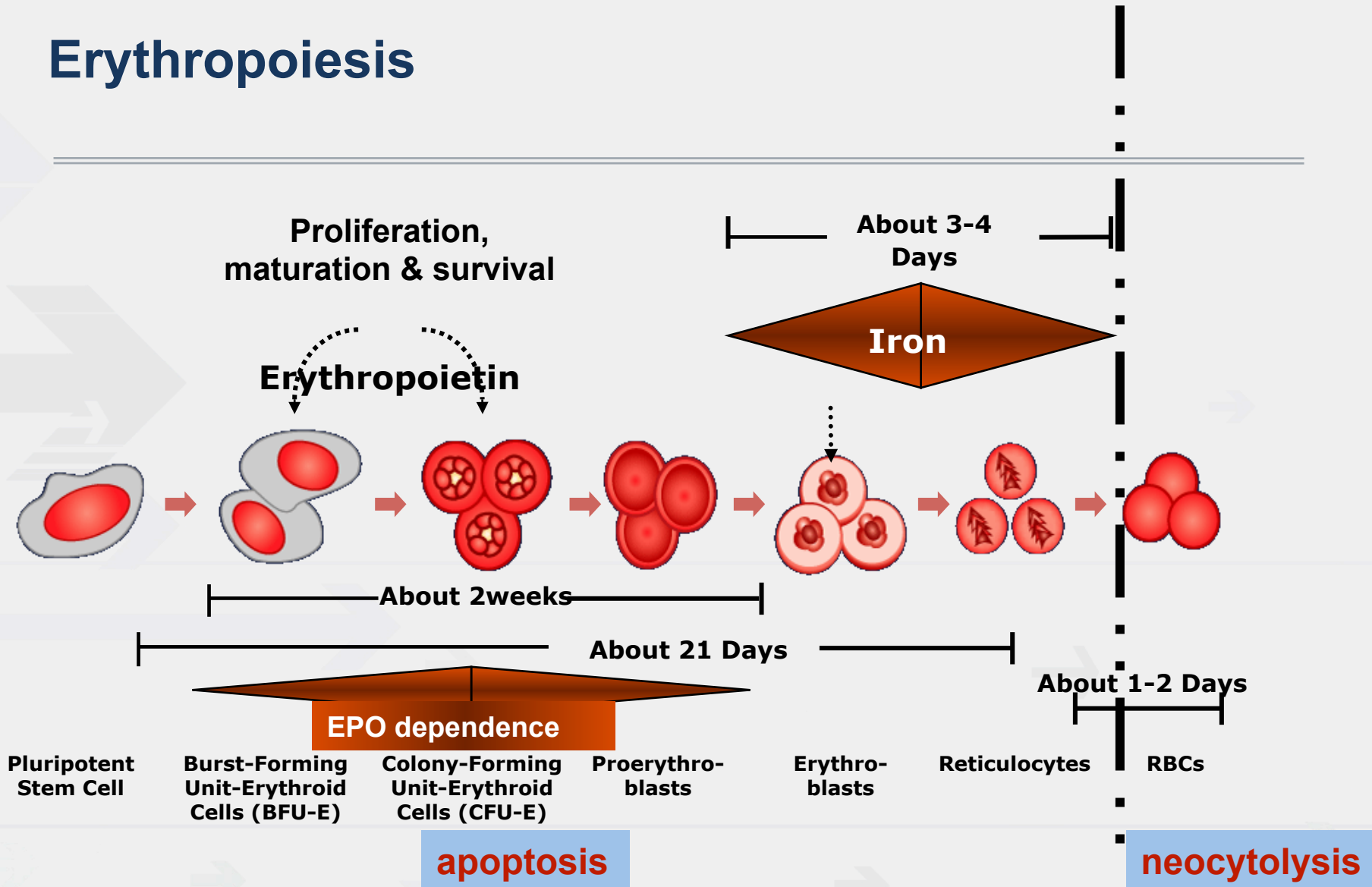
Baylor College of Medicine, Houston, TX, USA

School of Medicine UCLA, Los Angeles, CA, USA

Hadassah University Medical Center, Jerusalem, Israel

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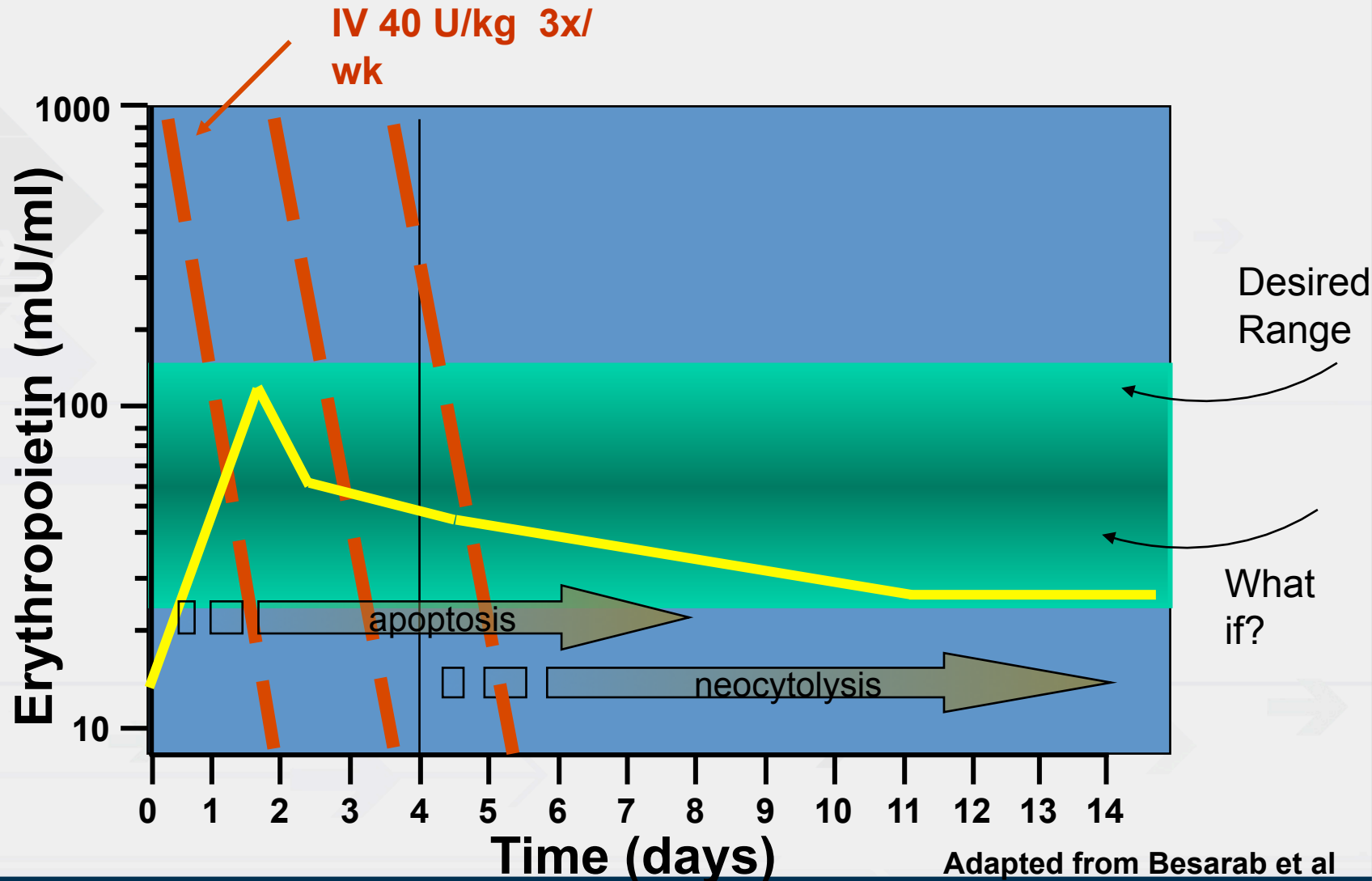
Erythropoiesis



Hillman RS, et al. *Red Cell Manual*, 7th ed. Philadelphia, PA: F.A. Davis Company; 1996:chap 1. Papayannopoulou T, et al. In: Hoffman R, et al. eds. *Hematology: Basic Principles and Practice*, 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:chap 20. Brock. *Iron Metabolism in Health and Disease*. W.B. Saunders Co; 1994

Epoetin alfa concentration – time profiles:

Route of administration (120 U/kg/wk)



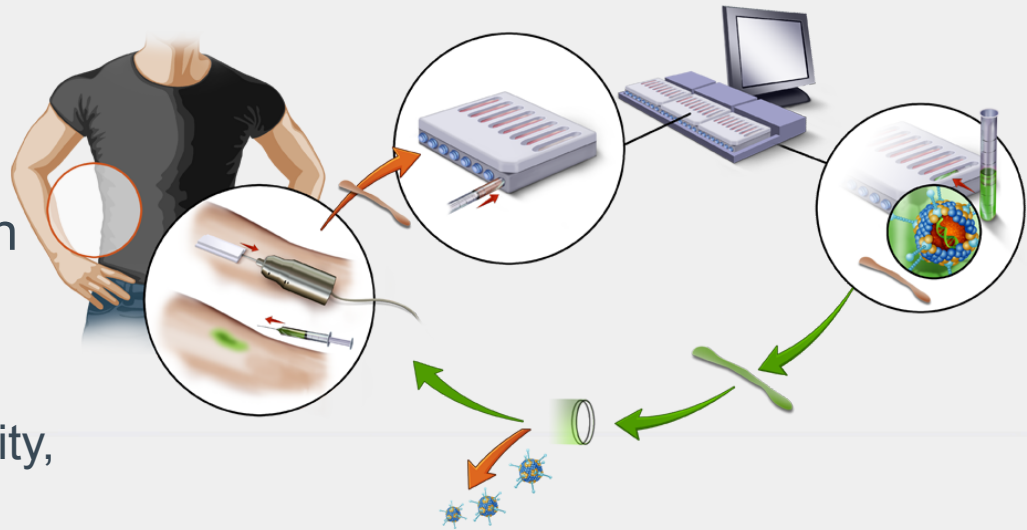
Adapted from Besarab et al
JASN 1992.

Biopump therapy:

Ex vivo genetic manipulation of dermal tissue structures for autologous production and delivery of therapeutic proteins

Therapy outline

- Harvesting
- Ex-vivo genetic manipulation using viral vector
- Pre- implantation analysis
- Secretion levels, Dosing, Viability, Sterility
- Subcutaneous implantation after 10-14 days
- Ablation or removal – to reduce dose, if required



EPODURE Phase I/II Clinical Trial

Phase I/II proof of concept, dose-ranging Study

- 15 to 20 anemic CKD patients
- three dose groups:
 - Low 18-25 IU/kg/day, Mid 35-45 IU/kg/day, High 55-65 IU/kg/day
- 6 months treatment, 6 months trial observation, possible non trial extension

Safety

- Ablate Biopumps, if needed, for:
 - Persistent Hb > 12 g/dl
 - Rate of rise Hb > 1g/dl over 2 wks
- Anti-EPO antibody surveillance

Key Endpoint

- Sustained elevation of hemoglobin
- Maintenance within therapeutic range (10-12 g/dl) with sufficient EPO dose

Methodology:

Anemic CKD stage 3-4 (MDRD-GFR) patients

- No systemic hematologic diseases
- No iron deficiency by TSAT and ferritin criteria
- Naïve or withdrawn from ESA > 30 days
- Baseline Hb
 - Naïve: average of at least 3 Hb values over 30 days
 - Previous ESA dependent: historic nadir Hb or projected nadir 100 days following ESA withdrawal

Measurement of Efficacy:

EPO level, Hb & HCT, reticulocyte counts, frequent during first 6 weeks, less frequent thereafter

Endpoints

- Hemoglobin response to EPODURE
- Duration of effect

Demographics:

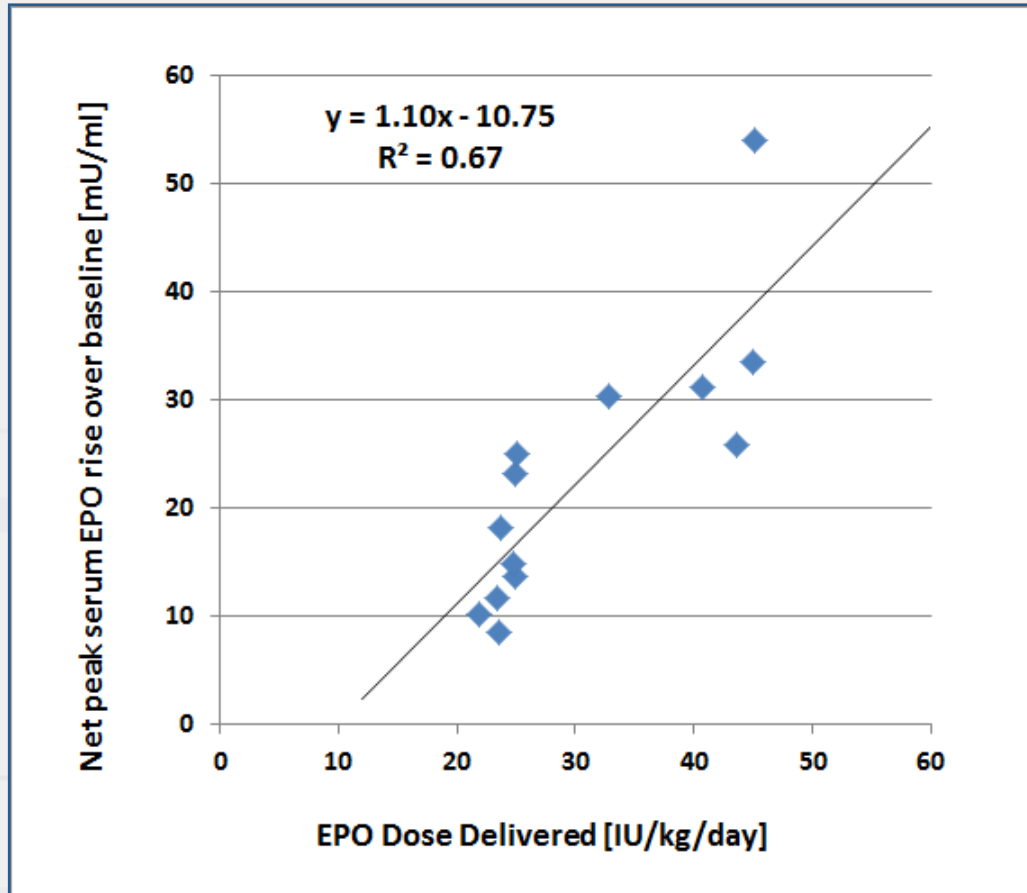
| | EPO Naïve N= 4 | EPO dependent N= 8 | Total N= 12 |
|--|-----------------------|-----------------------|-----------------------|
| Age [min-max ~] | 66 (min 48 max 82) | 56 (min 21 max 77) | 60 (min 21 max 82) |
| M/F [ratio] | 2/2 | 3/5 | 5/12 |
| Mean MDRD GFR [mL/min/1.73 m ² +/- SD] | 25 +/- 10 | 21 +/- 13 | 23 +/- 13 |
| Basal Hb/projected Hb [gm/dl] | 10.5 +/- 0.5 | 9.1 +/- 1.0 | 9.6 +/- 1.0 |
| Basal absolute reticulocytes [10 ⁹ /l] | 44 +/- 20 | 42 +/- 24 | 43 +/- 23 |
| Basal EPO levels [mU/ml] | 13 +/- 6 | 9 +/- 3 | 11 +/- 5 |
| Basal TSAT [%] | 22 +/- 9 | 27 +/- 6 | 25 +/- 8 |
| Basal Ferritin [ng/ml] | 211 +/- 101 | 213 +/- 84 | 212 +/- 90 |

Results: Safety

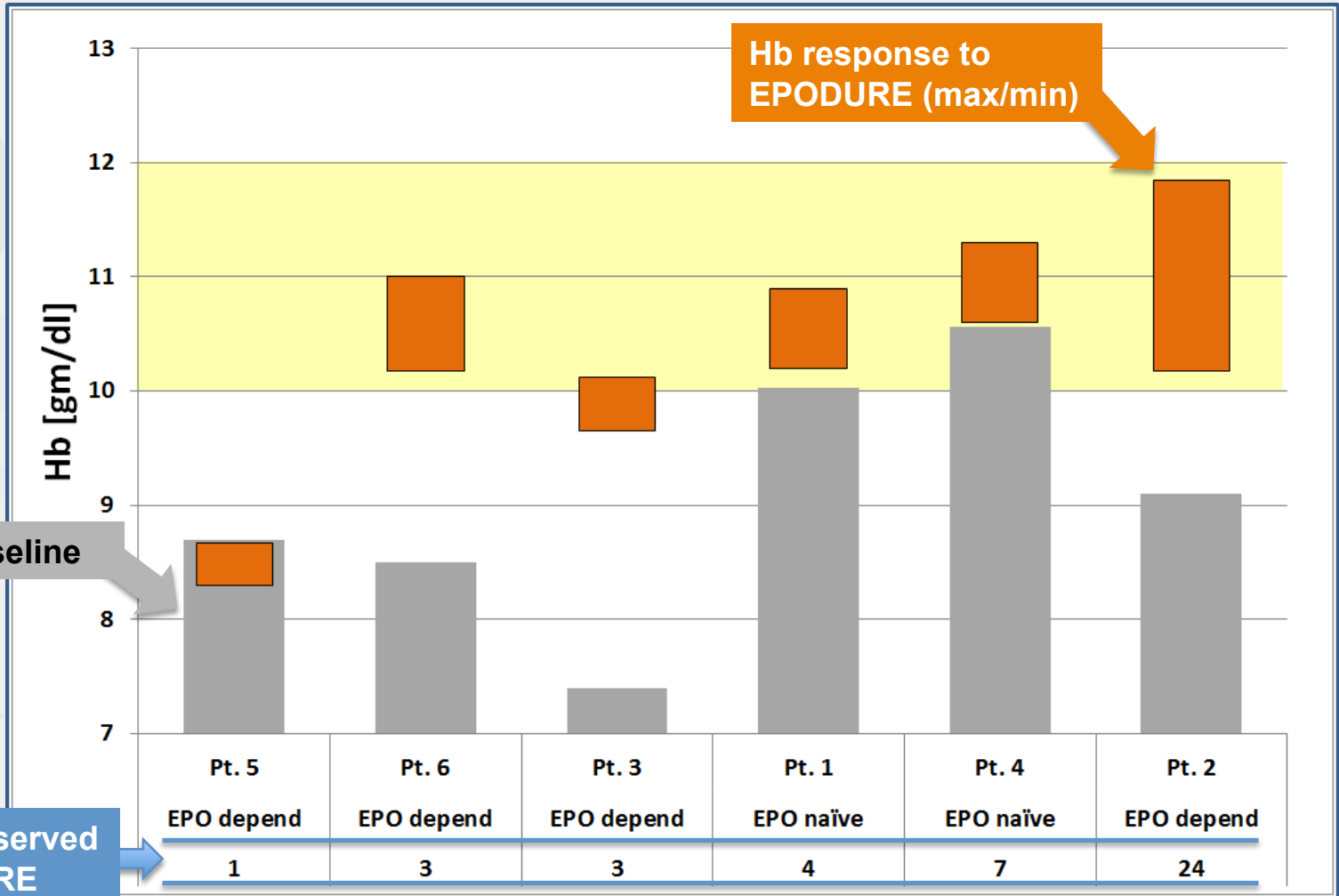
- **No adverse events in any patients treated**
- **Brief procedure, well tolerated**
- **No anti-EPO antibody formation**
 - All blood samples prior to and on therapy have been negative
- **No serum EPO levels to date exceeded 60 mU/ml**

Results: Doseability

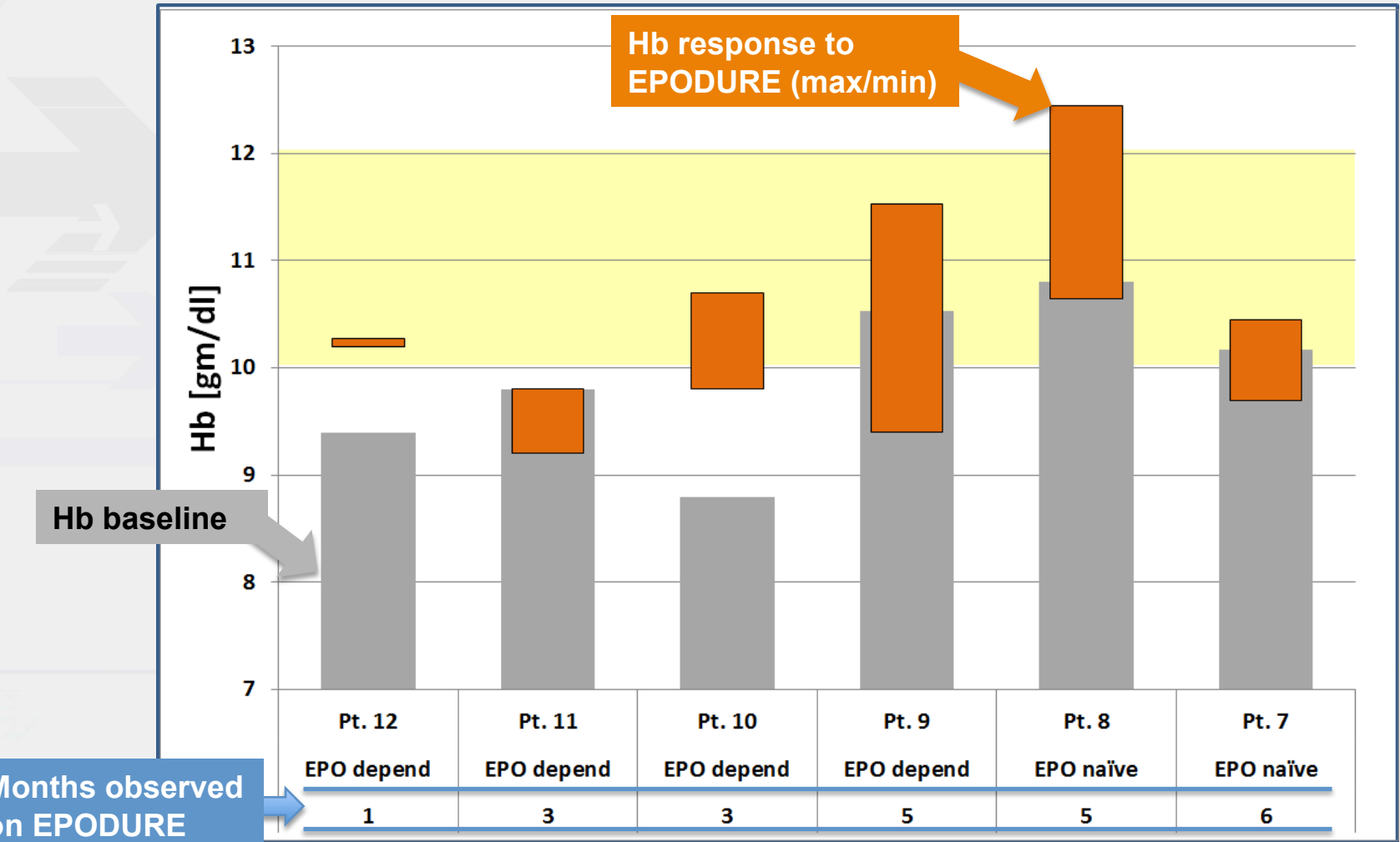
Correlation of net peak serum EPO rise to EPO dose administered



Results: EPODURE low dose group

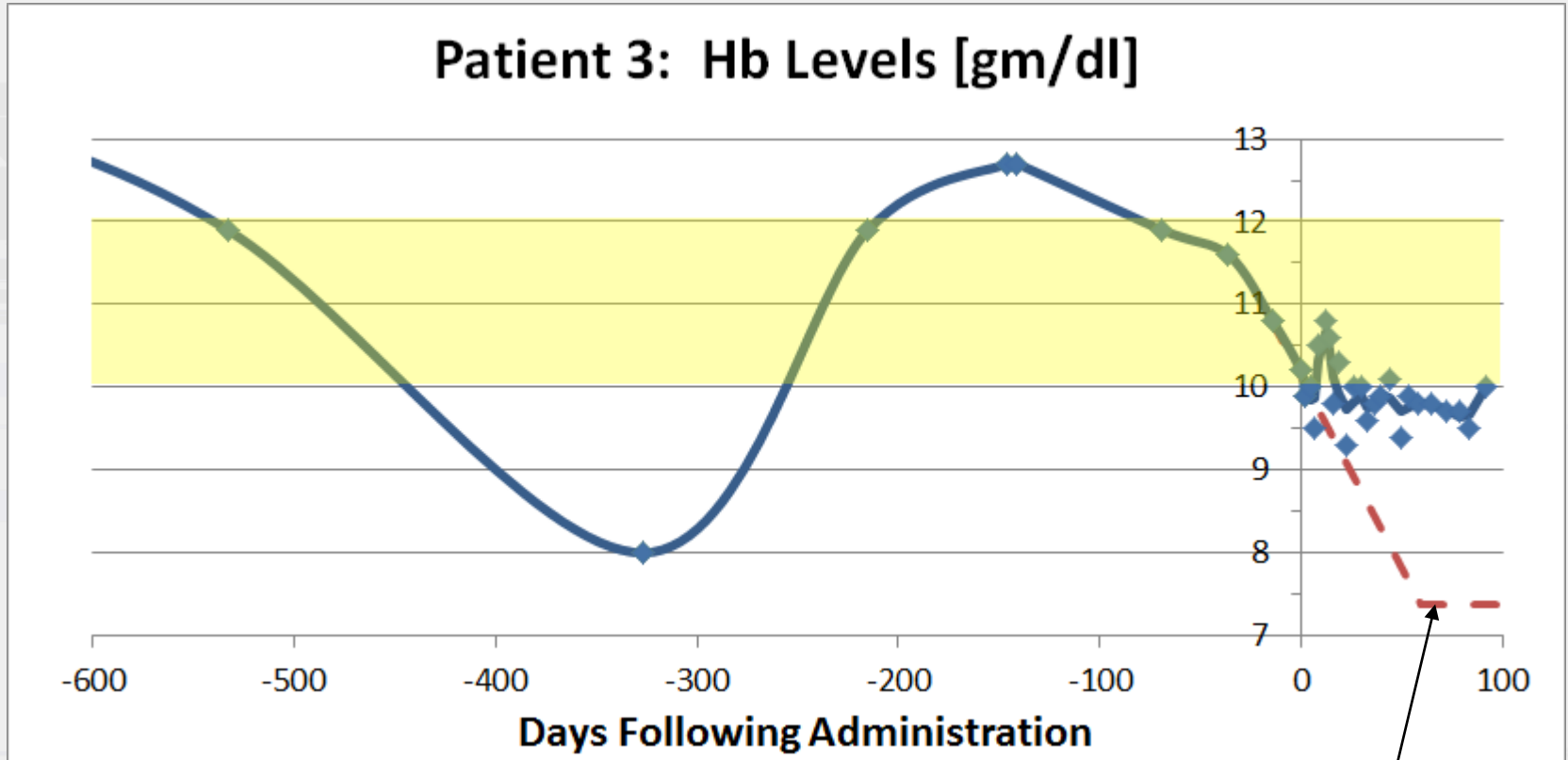


Results: EPODURE mid dose group



Results – Patient 3 (EPO Dependent)

Hemoglobin response: EPO injections versus EPODURE treatment



EPO Injections

Projected nadir:
ca 100 days after
last EPO injection

Conclusions

- EPODURE is safe and doseable; no antigenic response
- Clinical feasibility demonstrated
- Single EPODURE administration can raise and maintain Hemoglobin levels for up to 24 months without any injections of ESAs
- EPODURE has significant potential to become an effective interventional treatment – a paradigm shift

Acknowledgments

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