



Presentation to OBA RAC Meeting

March 8, 2012

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## Overview

1. EPODURE Product and Biopump platform technology
2. Anemia Management with EPODURE
3. Preclinical data
4. Clinical experience in Phase I/II CKD Study in Israel
5. Proposed Phase IIb Study





## Biopump: sustained protein production by autologous, intact dermis tissue



- **Micro-organ:** primary dermis tissue explant
- **Process:** Ex-vivo transduction with HDAd-EPO vector
- **Product:** EPODURE Biopump sustainably producing EPO





## Procedures on patient:

1. **Harvest microorgans** by needle biopsy from patient's dermis (parallel to skin)
2. **Implant** required number of Biopumps subcutaneously.
3. **Reversible** by excision.





## **Selection of HDAd as Gene Transfer Vector**

- 1. High transduction efficiency**
- 2. No viral genes**
- 3. Long term expression**
- 4. Safety**
  - **Lack of adaptive cellular immune response against transduced cells**
  - **Low frequency of integration, and limited to local excisable implant**
  - **No oncogenic events in over a decade of animal studies with HDAd**
  - **No oncogenic events in decades of human clinical trials with first generation Ad**





## **Need for Improved Anemia Management**

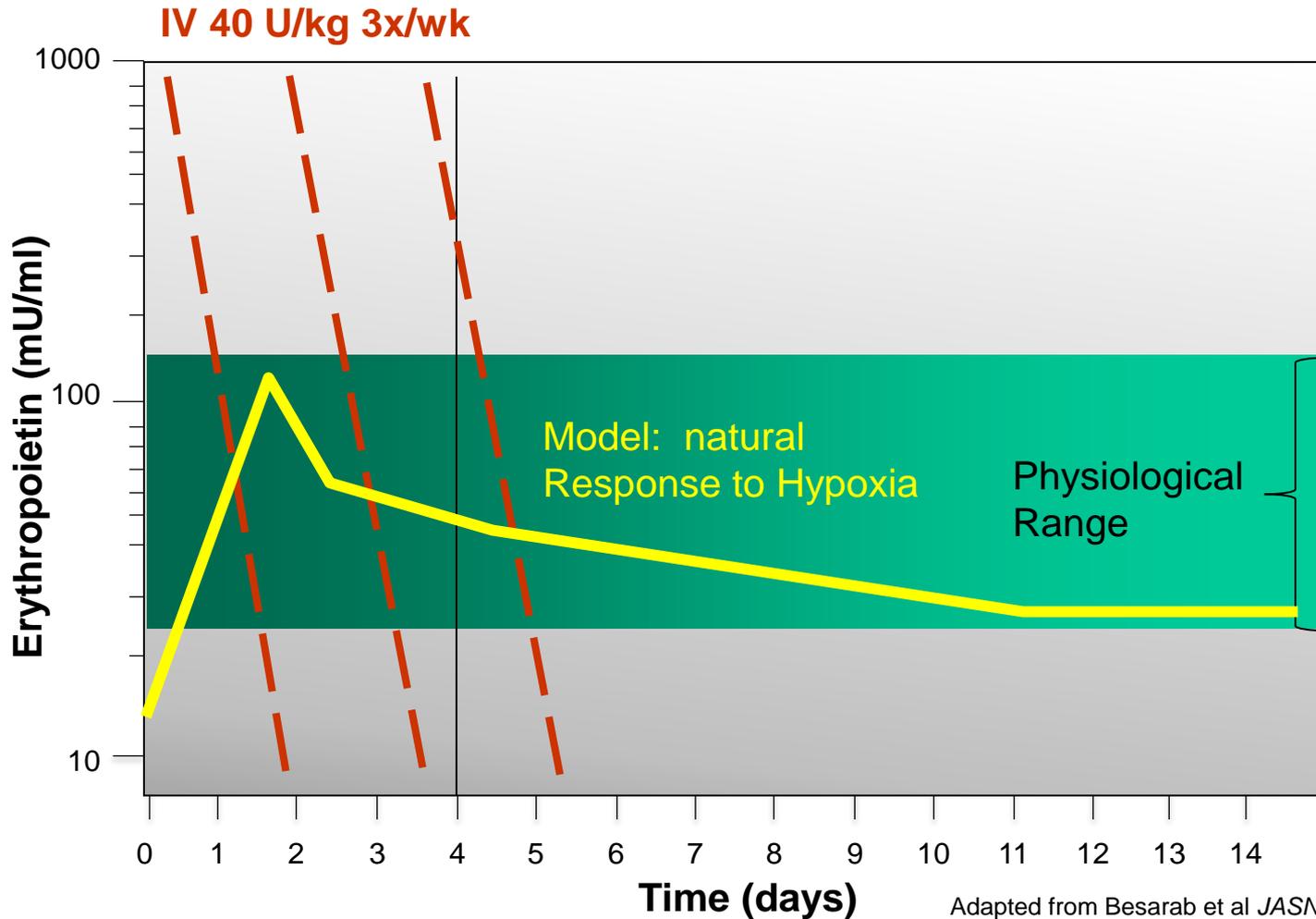
- 1. Better control of Hemoglobin while keeping EPO serum levels within physiological range**
- 2. FDA warning on Label for EPO use:**
  - Increases the risk of death, cardiovascular events
  - No method shown to maintain hemoglobin in range without incurring these risks
  - Use minimum ESA to keep hemoglobin in range
- 3. Superphysiological EPO with every injection**

**EPODURE Biopump aims to effectively address the need**



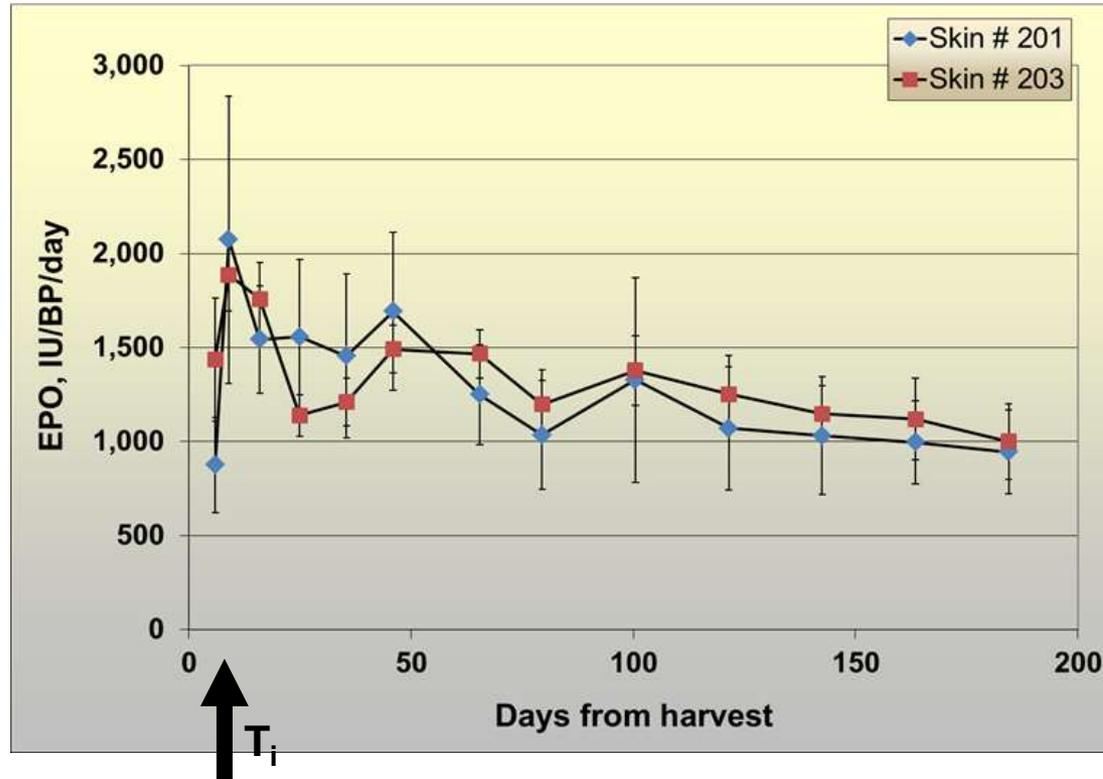
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# BACKGROUND: endogenous EPO response versus rHuEPO administration in dialysis





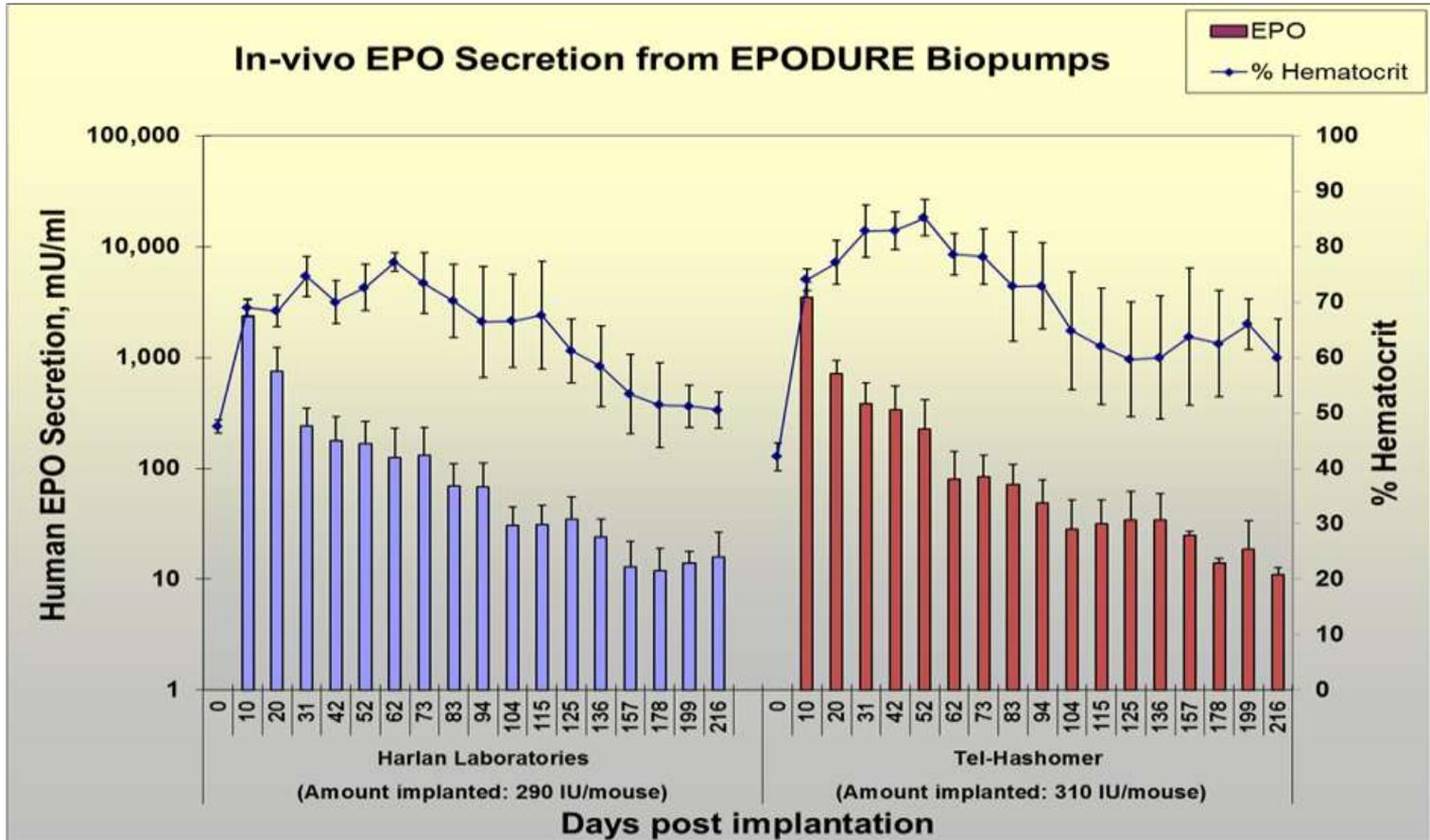
## Long term *in-vitro* EPO secretion from Biopumps



EPO secretion from dermal Biopumps prepared from 2 human skin samples according to the standard harvesting, transduction, and maintenance protocol. Values are Mean  $\pm$  STDEV; n=4 from each skin.



## Long term *in-vivo* physiological effect of EPODURE Biopumps implanted in SCID mice





## **EPODURE Phase I/II Clinical Trial (Israel)**

- **First in-human, safety and activity study**
- **Sequential dose escalation**
  - **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**
- **Patients: Chronic Kidney Disease stages III/IV (Pre-dialysis)**
  - **EPO dependent and EPO naive**
- **Endpoints**
  - **Safety: AE/SAE, procedure related events, routine labs, antibodies to EPO**
  - **Efficacy: EPO levels & Hb over time**



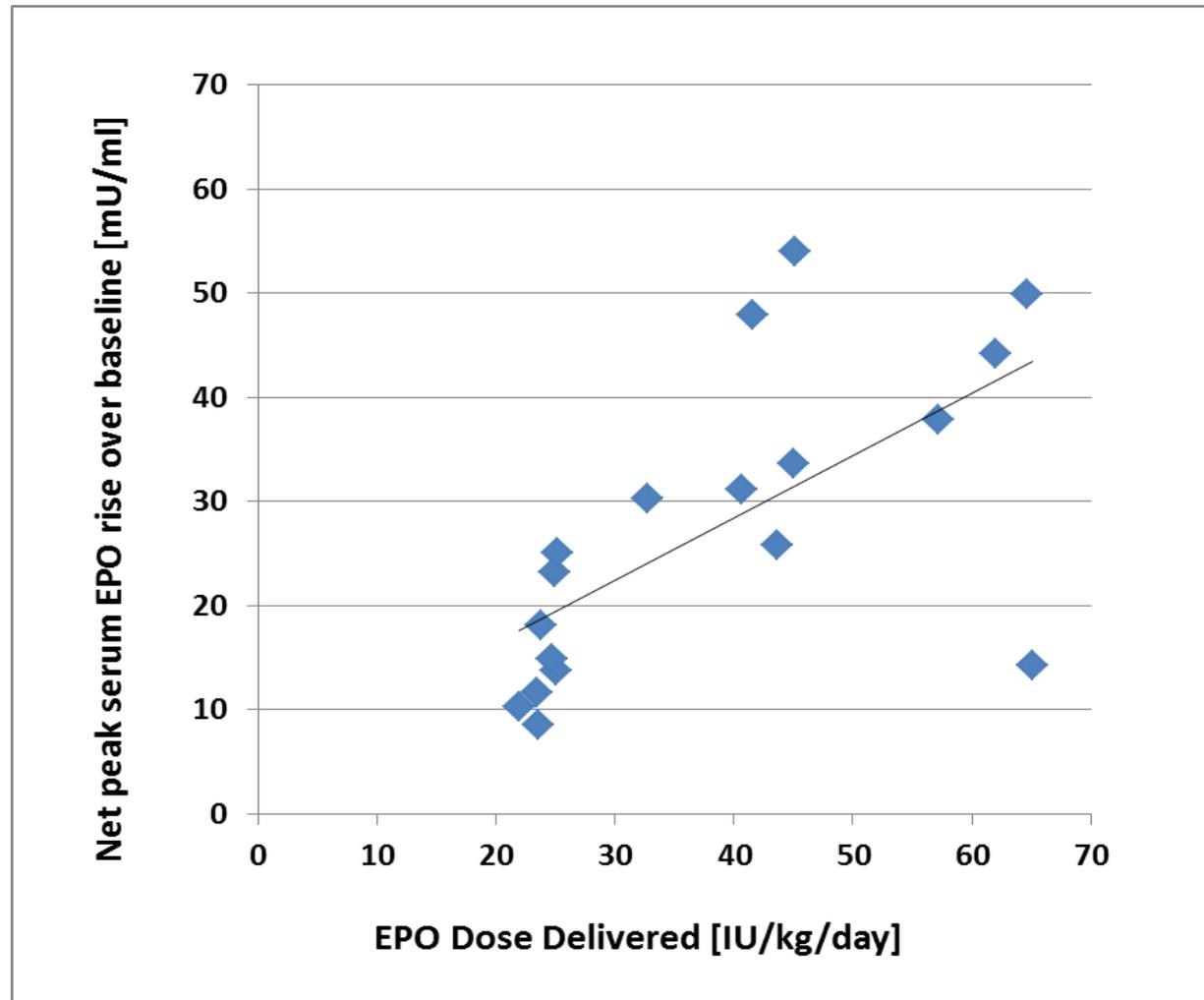


## Safety Results

- **No Product Related Serious Adverse Events**
- **All AEs**
  - AEs were reported in sixteen of the 18 subjects.
  - Serious AEs in 6 patients: anemia, inguinal hernia, TIA, worsening of renal failure, pneumonia, hyperkalemia, pulmonary edema, catheter placement, vomiting, nasal pharyngitis, headache
- **AEs Considered Related to excision or implantation occurred in 11 of 18 subjects**
  - Application site pruritus, implant site pain, incision site pain, hematoma
- **No anti-EPO antibody formation**
- **Overall, EPODURE Biopumps have been well tolerated and no specific safety signal has been identified.**



## EPODURE: EPO Dose Vs Net peak rise in serum EPO



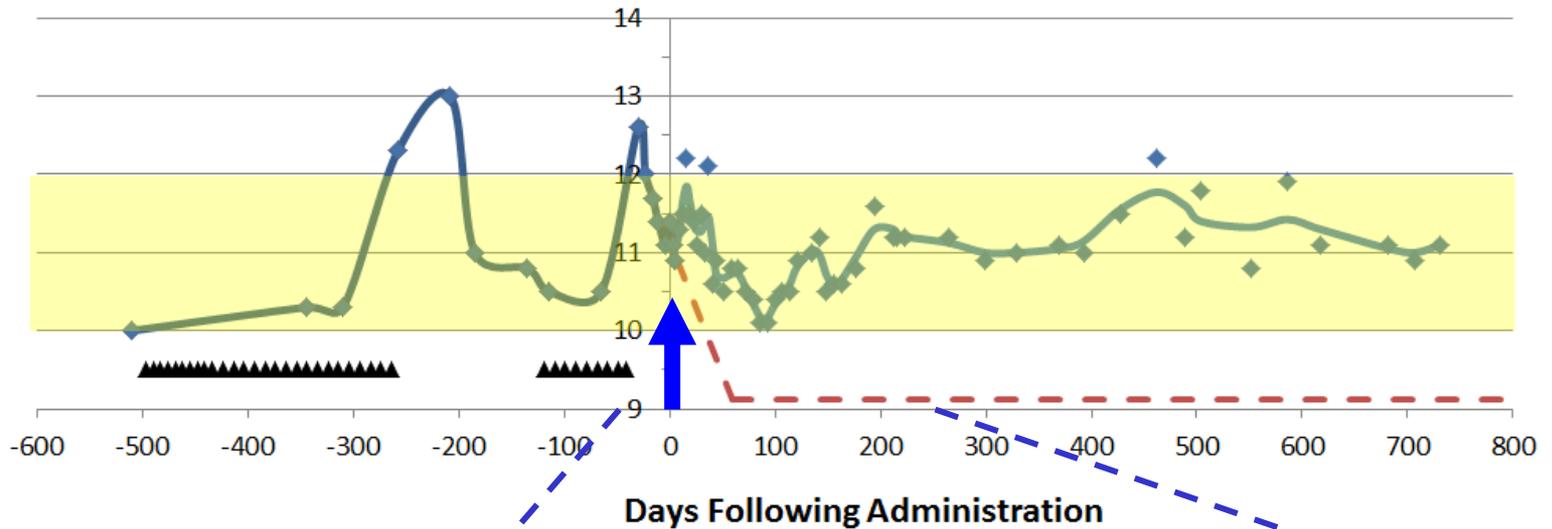


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## EPODURE in Stage 3 CKD EPO Dependent Patient:



Patient 2: Hb Levels [gm/dl]

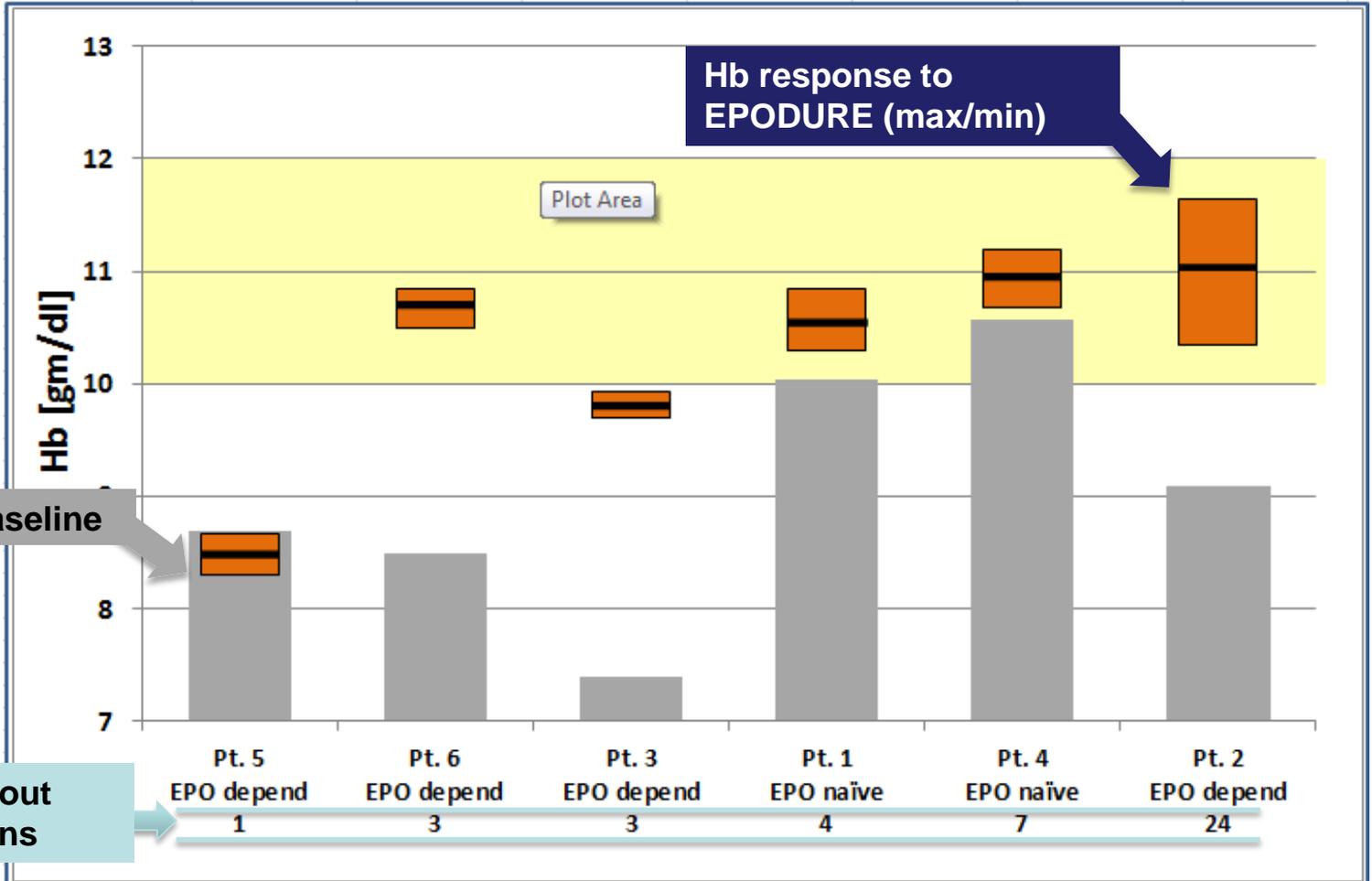


EPO Injections

EPODURE

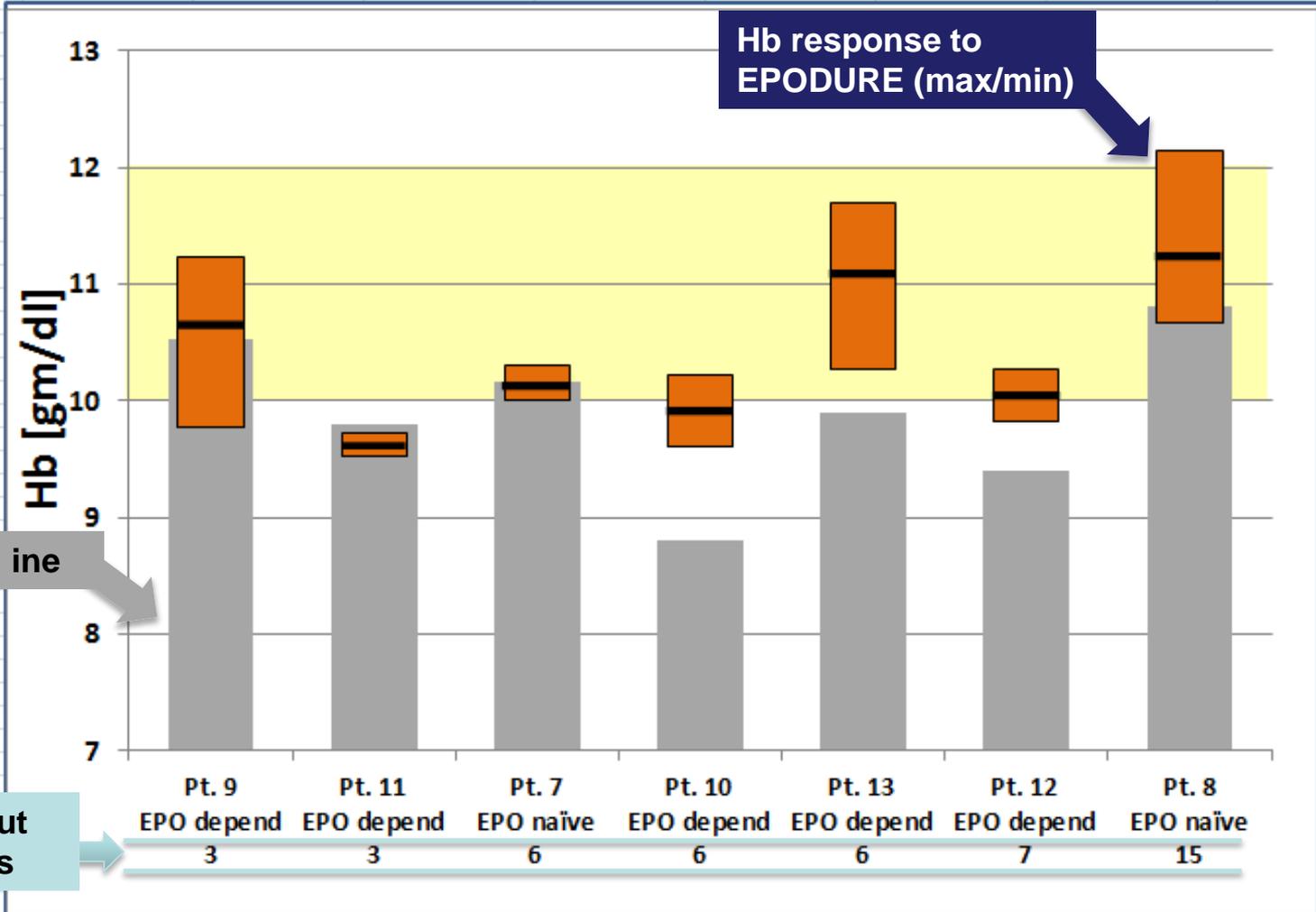


# Results: EPODURE low dose group





# Results: EPODURE mid dose group



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## Conclusions thru 17 patients treated in CKD study

- EPODURE is safe and doseable; no antigenic response
- Clinical feasibility demonstrated
- Single EPODURE administration can raise and/or maintain Hemoglobin levels for up to 36 months without any injections of ESAs
- Single EPODURE administration sustained Hb above baseline and above 9g/dl for:
  - >3 mo in 15/17 patients
  - >6 mo in 7/17 patients
- Serum EPO levels did not exceed 75 mU/ml



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**MG-001-04 is a Phase 2, Open Label, Randomized, Active Control, Multi-Center Study to Evaluate the Safety and Efficacy of EPODURE for Sustained Treatment of Anemia in Hemodialysis Patients**

**Marvin R. Garovoy MD**

**Chief Medical Officer**

**Medgenics, Inc**

**March 8, 2012**





## STUDY OBJECTIVES

- **To evaluate the efficacy of EPODURE treatment as assessed by:**
  - Maintenance of Hemoglobin levels within a target range defined as 9-11 g/dl
  - Avoidance of elevation of serum erythropoietin (EPO) levels above the upper limit of the normal physiological range, defined as a level  $> 200\text{mU/ml}$
- **To assess the safety of EPODURE treatment in the management of anemia in subjects with ESRD undergoing hemodialysis**
- **To assess the pharmacokinetics of erythropoietin in subjects treated with EPODURE**



## STUDY DESIGN

- **STUDY DESIGN:**

- Phase II, open label, randomized, active control, multi-center study

- **POPULATION**

- Adults diagnosed with anemia secondary to ESRD undergoing hemodialysis treatment for at least 90 days prior to screening and receiving stable doses of rHuEPO

- **SAMPLE SIZE AND RANDOMIZATION**

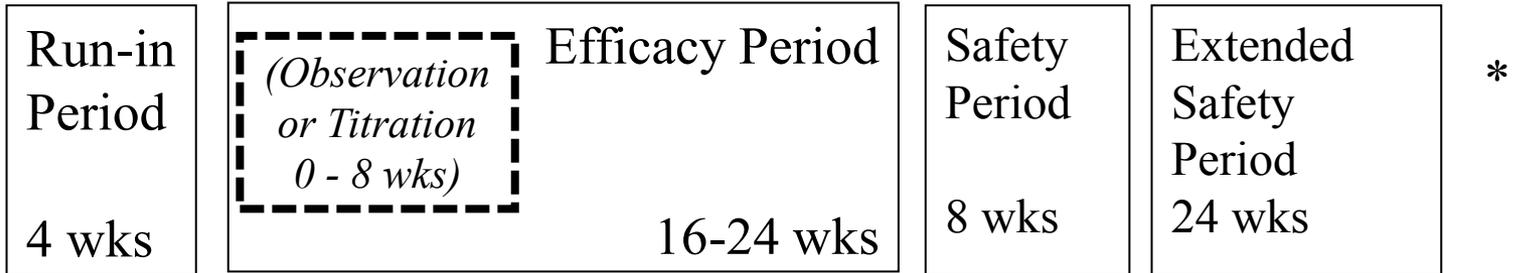
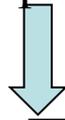
- 100 Randomized 3:2 : 60 to EPODURE , 40 to rHuEPO
- Stratified by baseline mean Hb





## STUDY DESIGN: PHASES OF STUDY

Biopump Implantation



*\*Subjects with functioning Biopumps will continue in 2 year Open label Long Term Safety Study*



## INITIAL DOSING

- **EPODURE Arm:** Biopump dose = average rHuEPO dose/day subject received during Run-In Phase
- **rHuEPO Control Arm:** continue to receive standard rHuEPO dose to maintain Hb level between 9-11 g/dl
- ***After initial 10 subjects have completed 4 weeks of treatment, data will be analyzed to determine if initial dosing algorithm requires modification based upon observed Hb response***



- **Primary Efficacy Endpoint:**
  - Percent of subjects with Hb maintained within range of 9-11 g/dl during Efficacy Assessment Period
- **Key Secondary Efficacy Endpoints:**
  - Number of occurrences/AUC per subject of serum EPO levels > 200 mU/ml during Titration and Efficacy Assessment Period
  - Percent of subjects who meet primary endpoint without need for any rHuEPO supplementation
- **Safety** – Adverse events, hematology, blood chemistry, Anti-Erythropoietin antibodies, physical exam, assessment of wound healing status post implantation, cardiovascular events



## SAFETY: DOSE REDUCTION

### ■ EPODURE arm

- If Hb level of  $\geq 12.0$  g/dl **over 2 calendar weeks**, at any time, dose will be reduced by 25-50% by excision of one or more Biopumps
- If Hb is  $\geq 13.0$  g/dL on any **single** assessment, at any time, it will be repeated at the next dialysis session and if it remains  $\geq 13.0$  g/dL, Biopumps will be excised to achieve a 50% reduction

### ■ rHuEPO arm

- Hb measurements above 11.0g/dl over 2 calendar weeks, will result in a reduction of the administered rHuEPO dose based on actual Hb and rate of rise
- If Hb is  $\geq 12.0$  g/dL rHuEPO will be held and Hb assessed weekly. When Hb falls below 11.0 g/dL, rHuEPO will be resumed at a dose 50% less than the previous dose.



## SAFETY: rHuEPO “RESCUE THERAPY”

- **Both Arms (ALL Patients):**
  - If Hb drops below 9 g/dl over 2 calendar weeks or falls below 8 g/dl on any single measurement, supplemental rHuEPO will be administered
  - When Hb returns to the target range on 2 consecutive weekly assessments, the rHuEPO injections may be stopped or reduced in dose



## BIOPUMP EXAMINATION

- **Biopumps removed for any reason will undergo:**
  - Histologic examination
  - Production of EPO protein by immunochemistry
  - Test (under development) for
    - Vector DNA
    - EPO mRNA



- **Safety**
  - **Adverse events**, hematology, blood chemistry and Anti-Erythropoietin antibodies, physical exam and assessment of wound healing status post implantation
  - Assess ***specific cardiovascular safety events*** that could be associated with administration of rHuEPO
    - **Cardiovascular events:** Stroke or TIA, Myocardial Infarction, Congestive Heart Failure, Myocardial ischemia, Peripheral arterial disease, Vascular access thrombosis



## Safety: Data Safety Monitoring Board and Stopping Rules

### Data Safety Monitoring Board (DSMB)

- The DSMB will review all SAEs and recommend any changes to study conduct including stopping the study or modifying safety monitoring.
- *If study drug is stopped, all subjects will continue to be followed for safety. Safety data will be assessed and discussed with CBER, FDA prior to resumption of study activities.*

### Stopping Rules: All enrollment and further study drug administration to new subjects will stop if any of the following events occur

- Death attributed to study drug
- A grade 3 or higher adverse event attributable to study drug that leads to removal of EPODURE Biopump.



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## **Medgenics Team at RAC**

**Stephen Bellomo VP**

**Butch Dellio COO**

**Nir Shapir, PhD VP R & D**

**Ehud Shoshani, MD VP Clinical Affairs**

**Philip Ng, PhD Assoc Prof Molecular Genetics, Baylor College**

**Geoffrey Block, MD, Denver Nephrology**

**Anatole Besarab MD (via phone) Chief Nephrology, Henry Ford**

**Amos Panet, PhD Prof. Biology, Chief of Virology Hadassah**

**Andra Miller PhD Biologics Consulting Group**

**Barbara Matthews, MD BioDirect**





## EPO Response to 2 EPODURE Administrations

