



**BIO 2011**

*The Diabetes Forum:*

*Emerging Strategies, Challenges, and Partnerships*

June 29, 2011

Washington, D.C.

**Getting Treatments and Preventions**

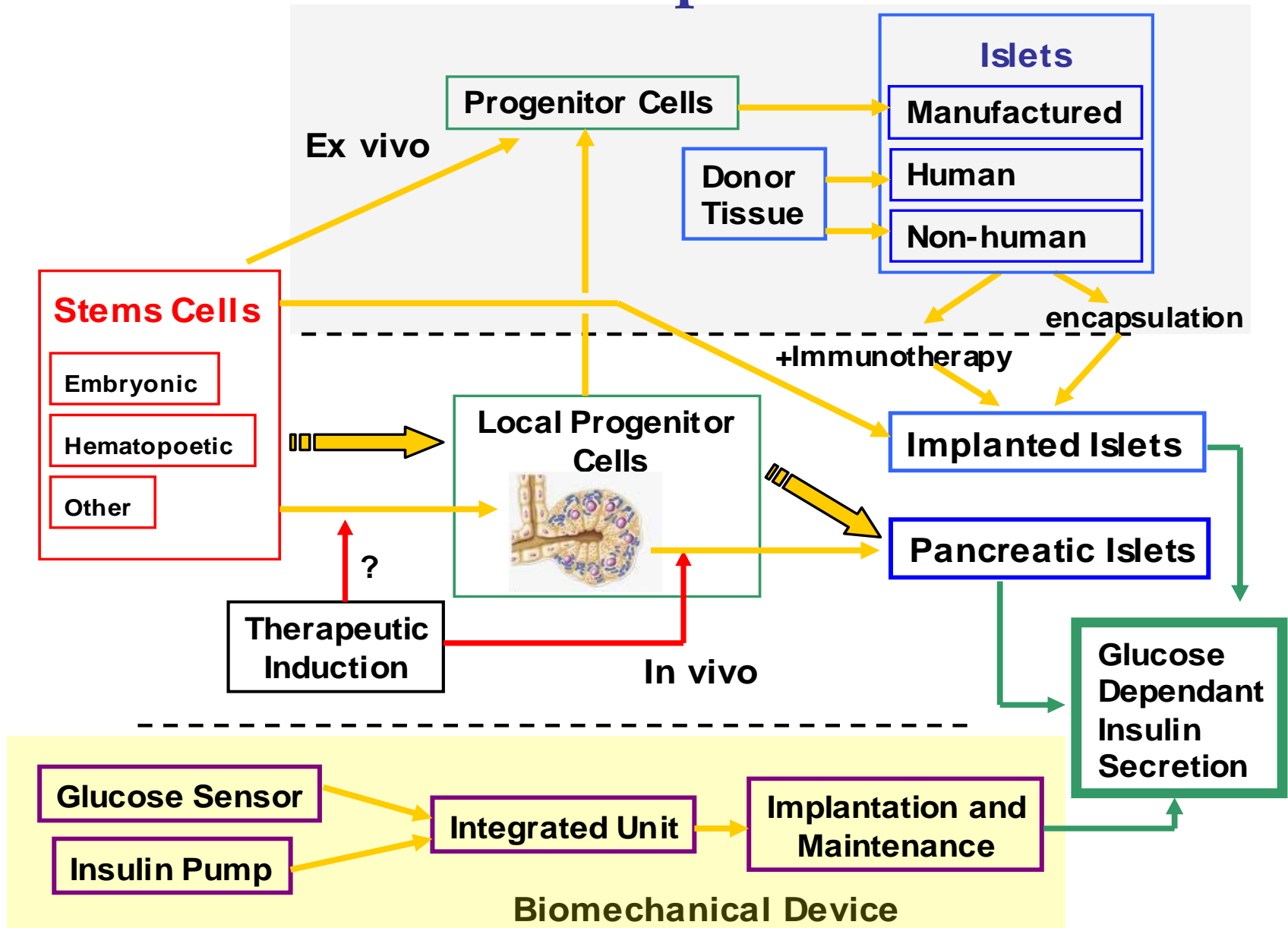
**Approved for T1DM –**

**Progress Made and Challenges Remaining**

**Alexander Fleming, MD**

**Kinexum**

# Approaches to Restore Auto-Regulated Insulin Secretion in People with T1DM



# **Draft Guidance for Industry and Food and Drug Administration Staff**

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## **The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Low Glucose Suspend (LGS) Device Systems**

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

# **Draft Guidance for Industry and Food and Drug Administration Staff**

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## **Draft Guidance for Industry and FDA Staff: Artificial Pancreas Systems – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications**

*DRAFT GUIDANCE*

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# Coming by end of 2011?

## Draft Guidance for Industry and Food and Drug Administration Staff

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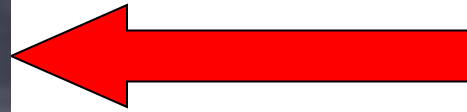
### Draft Guidance for Industry and FDA Staff: Artificial Pancreas Systems – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications

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# T1DM Therapeutic Targets

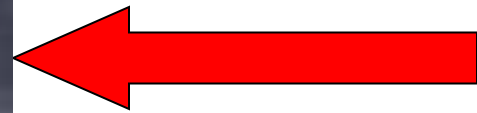
**New Onset  
T1DM**



**Established  
T1DM**



# T1DM Prevention Targets



**High Risk  
Populations**



**General  
Population**



# FDA – the Enemy?





# The NEW ENGLAND JOURNAL of MEDICINE

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PERSPECTIVE

Volume 351:1707-1709

October 21, 2004

Number 17

## Failing the Public Health — Vioxx, Merck, and the FDA

*Eric J. Topol, M.D.*

On May 21, 1999, Merck was granted approval by the Food and Drug Administration (FDA) to market rofecoxib (**Vioxx**). On September 30, 2004, after more than 80 million patients had taken this medicine and annual sales had topped \$2.5 billion, the company withdrew the drug because of an excess risk of myocardial infarctions and strokes. This represents the largest prescription-drug withdrawal in history, but had the many warning signs along the way been heeded, such a debacle could have been prevented.



# The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Volume 356:2457-2471 June 14, 2007 Number 24

[vious](#)

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## Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

*Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.*

### ABSTRACT

**Background** Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

**Methods** We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability

# T1DM vs. T2DM

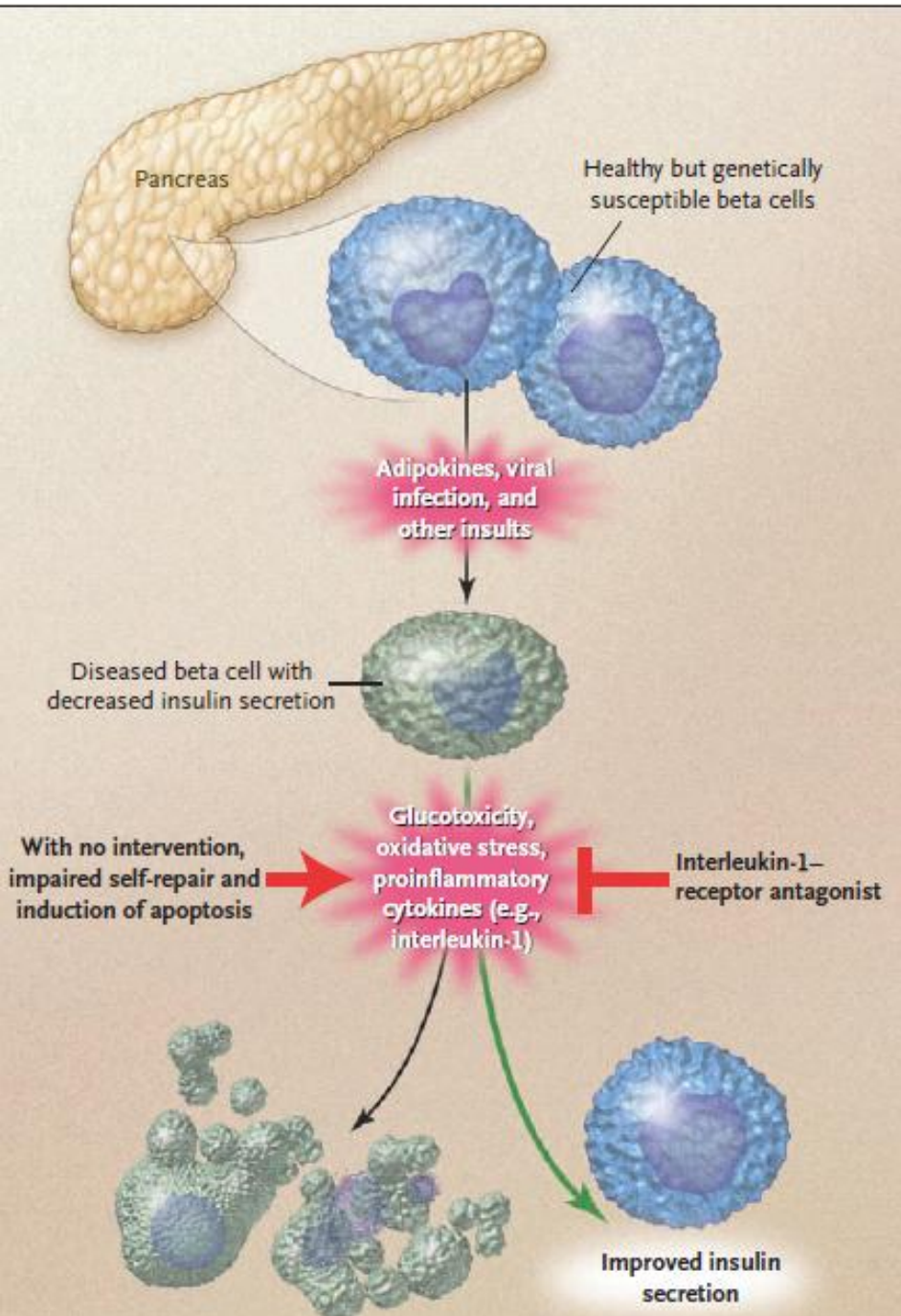
## Tale of Two Indications

	T2DM	T1DM
Primary Endpoint	HbA1c	C-Peptide
Total patient N	>8,000	~1,000
Phase 3 studies N	5	2
Study duration	6 months-3 years	~2 years
CV safety study	yes	no
Cost of Phase 3 Program	~\$1 billion	>\$200 million
Priority Review	No	Probably
High unmet clinical need	Not so much	Yes

Opportunity for  
Some therapies:

**Inflammation:**

**Etiologic  
Convergence of  
T1 and T2DM**



# **Why have T1DM therapies gone into Phase 3?**

**The goal posts are now  
understood.**

# diabetes

*Diabetes* 53:250-264, 2004

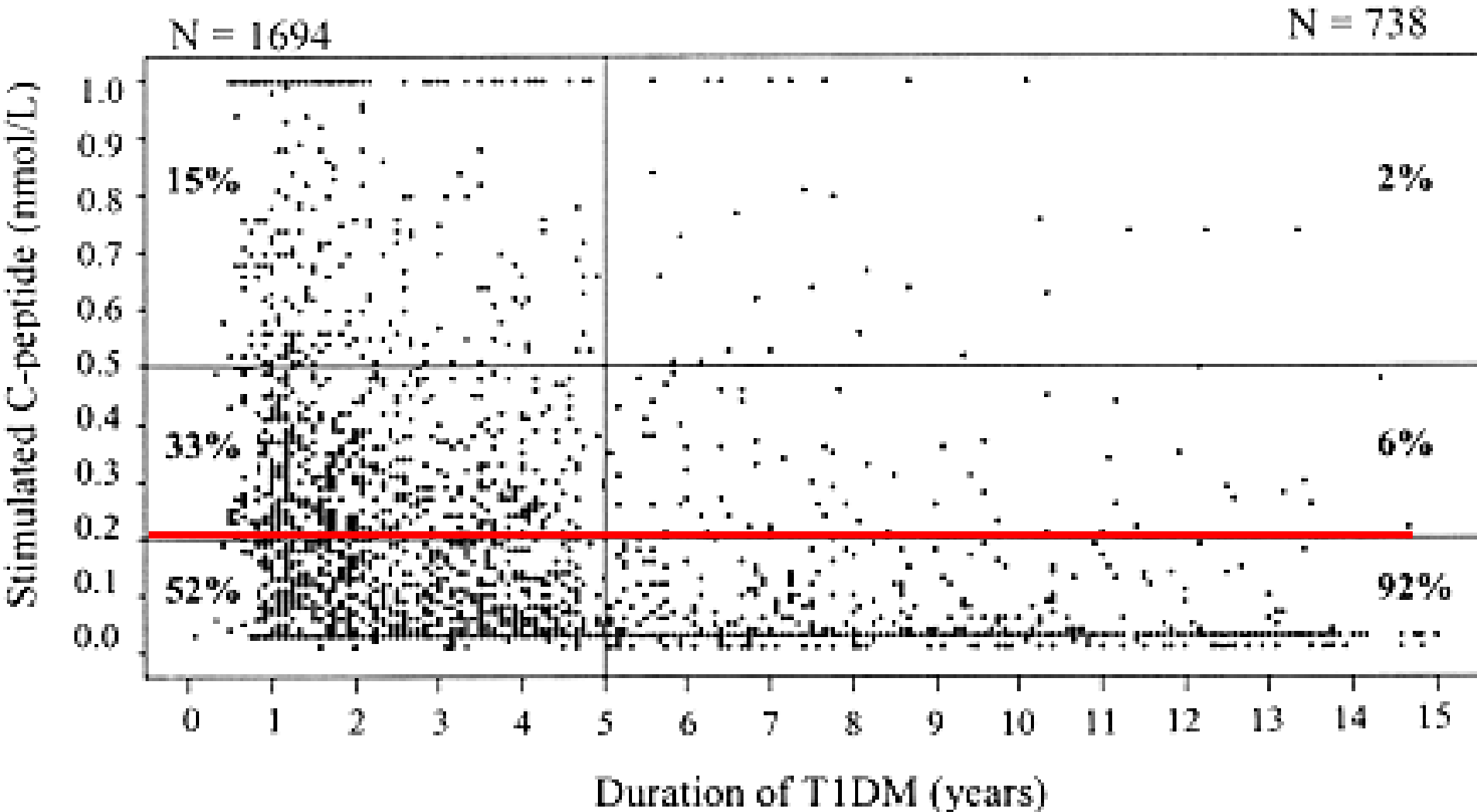
## **C-Peptide Is the Appropriate Outcome Measure for Type 1 Diabetes Clinical Trials to Preserve $\beta$ -Cell Function Report of an ADA Workshop,**

21-22 October 2001

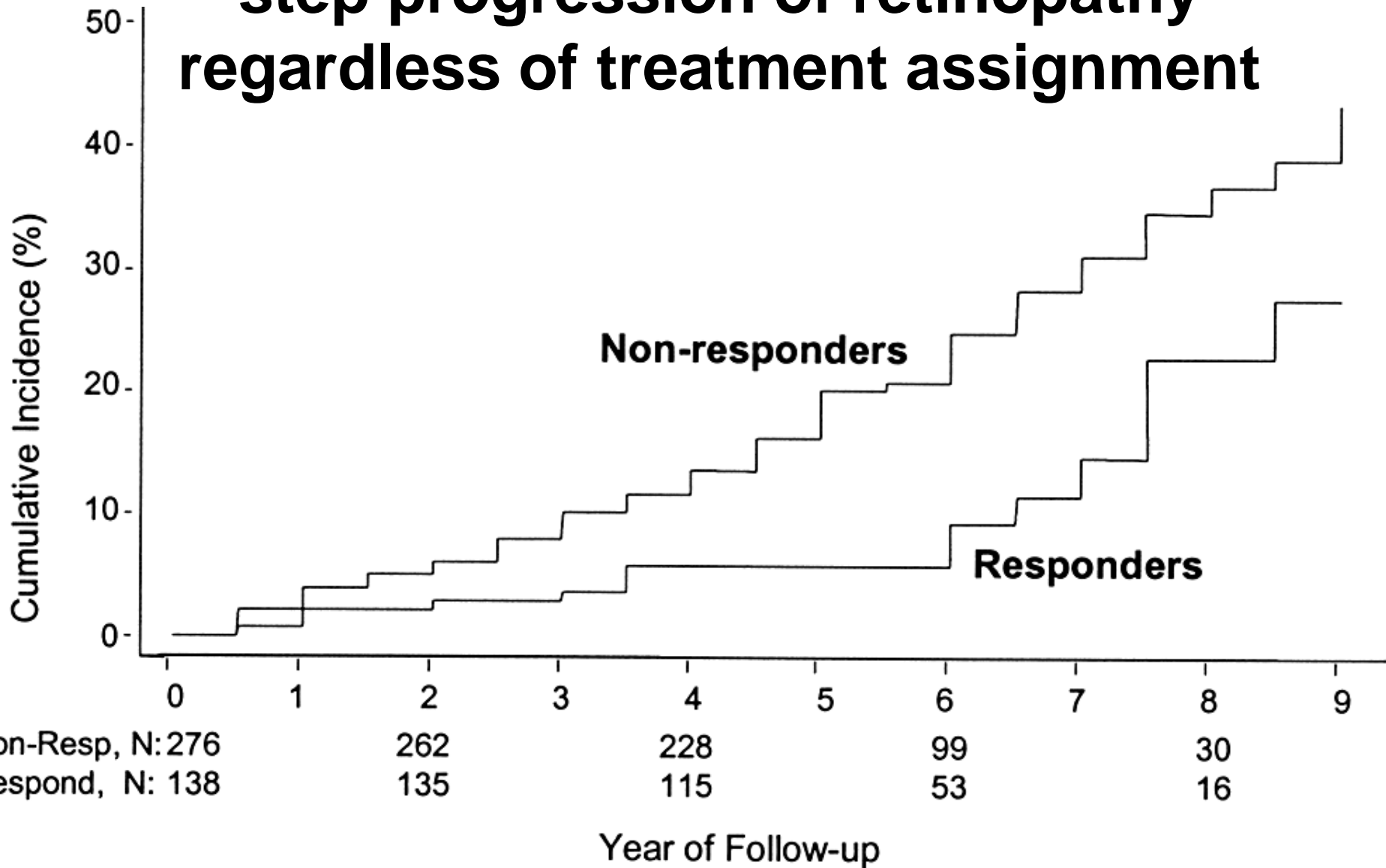
Jerry P. Palmer<sup>1,2</sup>, G. Alexander Fleming<sup>3</sup>, Carla J. Greenbaum<sup>4</sup>, Kevan C. Herold<sup>5</sup>, Lisa D. Jansa<sup>3</sup>, Hubert Kolb<sup>6</sup>, John M. Lachin<sup>7</sup>, Kenneth S. Polonsky<sup>8</sup>, Paolo Pozzilli<sup>9</sup>, Jay S. Skyler<sup>10</sup>, and Michael W. Steffes<sup>11</sup>

# Duration of T1DM and endogenous insulin secretion at entry into DCCT

N=2342



# Cumulative incidence of three or more-step progression of retinopathy regardless of treatment assignment



# **Current Focus of T1DM Therapeutic Development**

**Preserving remaining insulin  
secretion in new onset disease**

# Indication for immunomodulator

**ILOFEND<sup>®</sup>**

**R<sub>x</sub>**

(~peptide)

**Injection**

## INDICATION

**IloFend<sup>®</sup> is indicated for the preservation of endogenous insulin secretion in patients with recently diagnosed type 1 diabetes mellitus.**

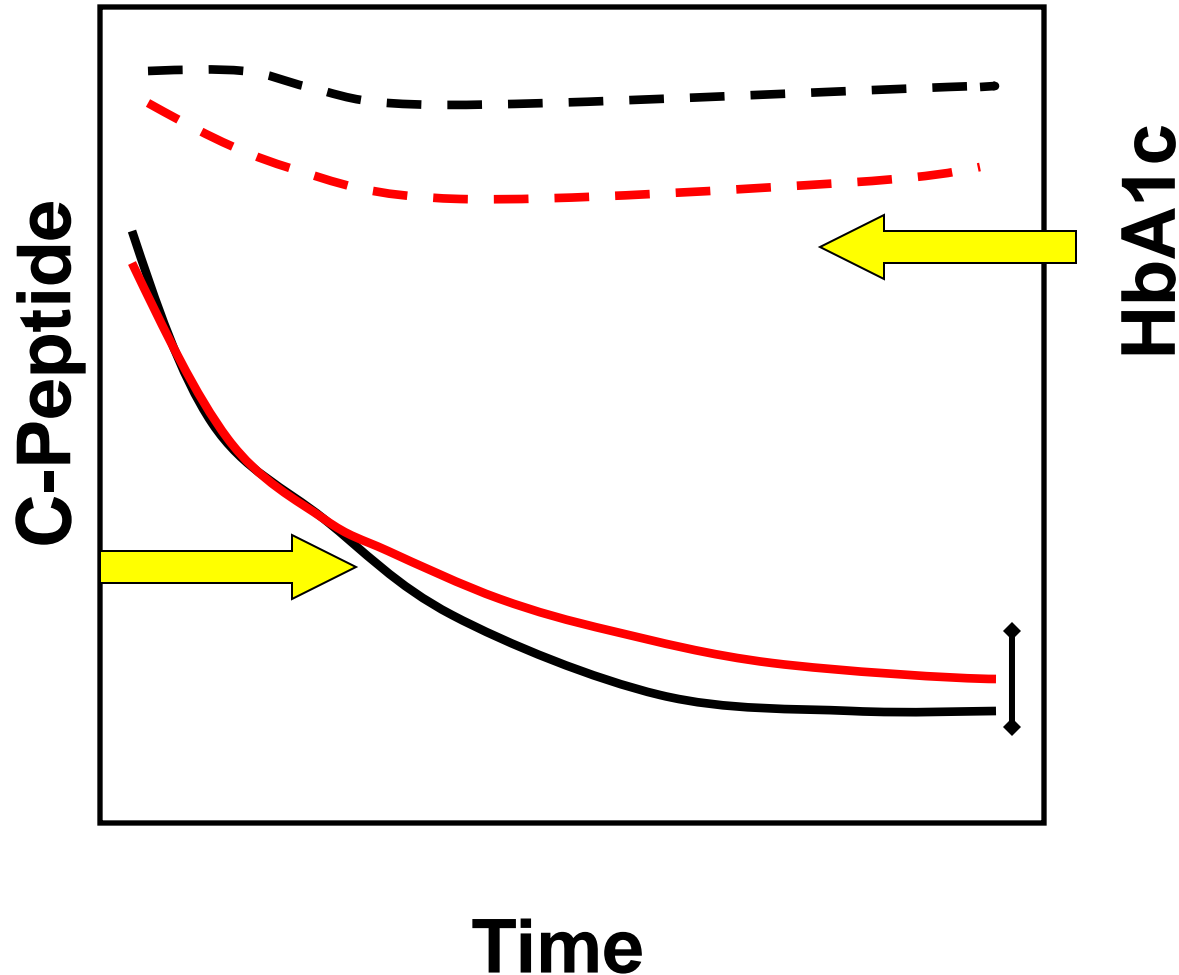
# Study Design

- **Primary endpoint: Endogenous insulin secretion as reflected by stimulated C-peptide levels**
- **≥12-24 month double-blind**
- **Treat to glycemic target**

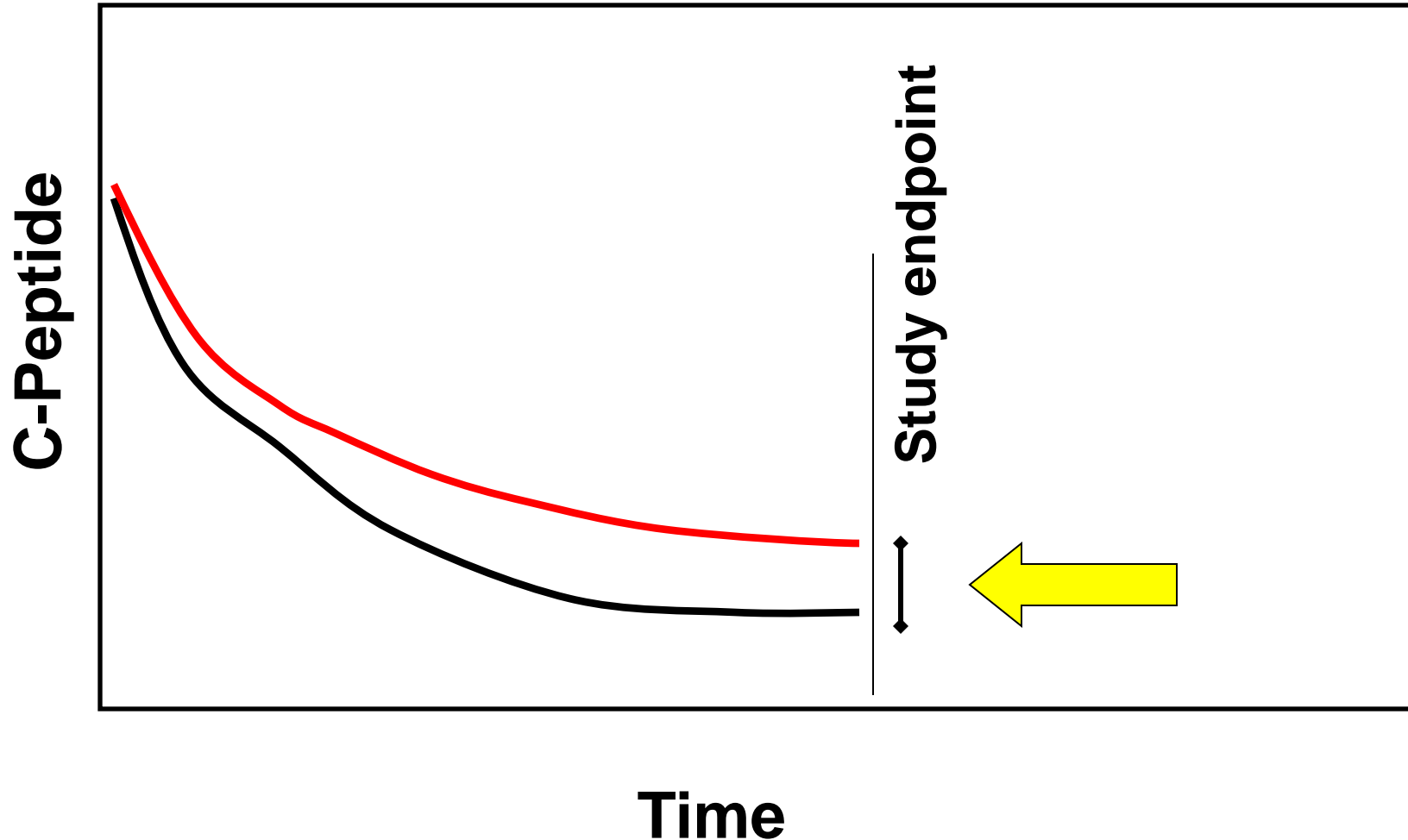
# Secondary endpoints

- **HbA1c**
  - FDA now understands that this is a measure of the trial and not of efficacy
- **Insulin dose**
  - Derivative of primary effect on preservation
- **Rates of hypoglycemia and complications**
  - Reductions are the ultimate expected benefits
  - Challenging to demonstrate prior to approval

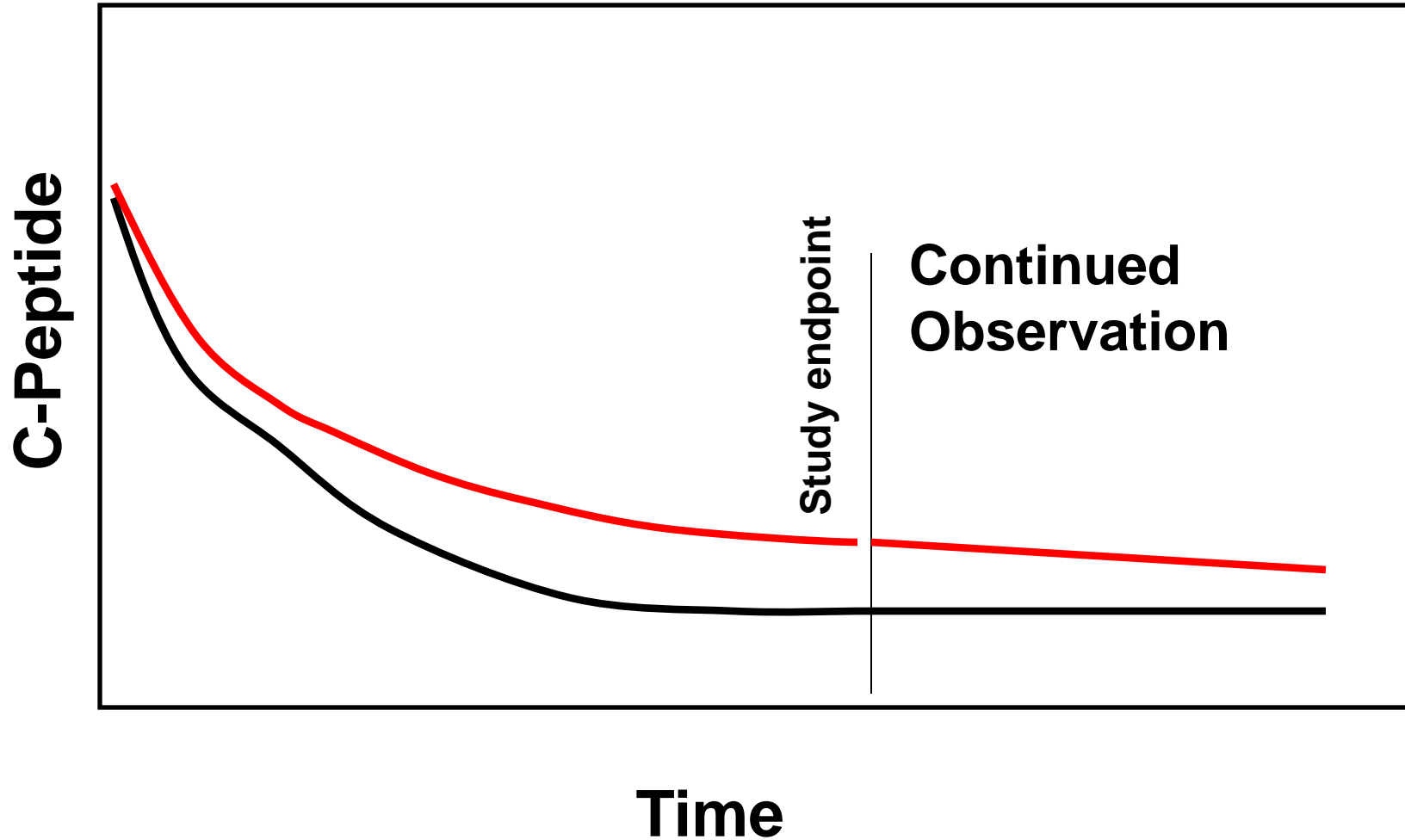
# Importance of A1c as a reflection of trial integrity and not efficacy:



# Important consideration – Treatment effect size



# Important consideration-- Durability



# Other Considerations

- **Mechanism of Action – Vaccine paradigm**
- **Dose Optimization**
- **Indicated Populations**
- **Durability of Effect**

**The regulatory basis of approval for  
 $\beta$ -cell preserving agents  
[and probably any diabetes therapy]**

- **On overall benefit to risk relationship**
- **Will be provisional in the sense that post-approval follow up and controlled studies will be required**
- **Drug product label will evolve**

# Going beyond treating early onset T1DM

## Regeneration and Combination Approaches

# Indication for islet regeneration agent

**BETAGEN<sup>®</sup>**

**R<sub>x</sub>**

**Cryptoilotropin (peptide)**

**Injection**

## **INDICATION**

**BetaGen<sup>®</sup> is indicated for the restoration of endogenous insulin secretion in patients with type 1 and 2 diabetes mellitus.**

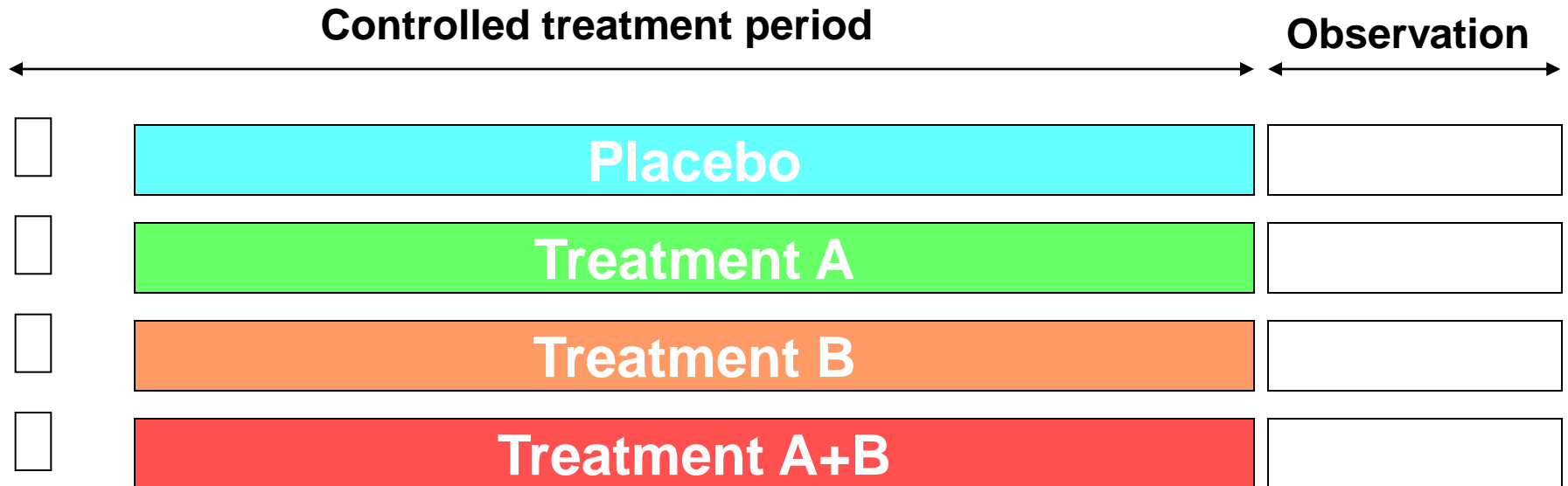
# Therapies for restoring lost islet function are –

- **Foreseeable**
- **Could be cellular or pharmacologic**
- **Will benefit from combination with immunotherapy**
- **Will give the prospects of treatment to all people with T1DM and T2 patients failing on oral therapy**

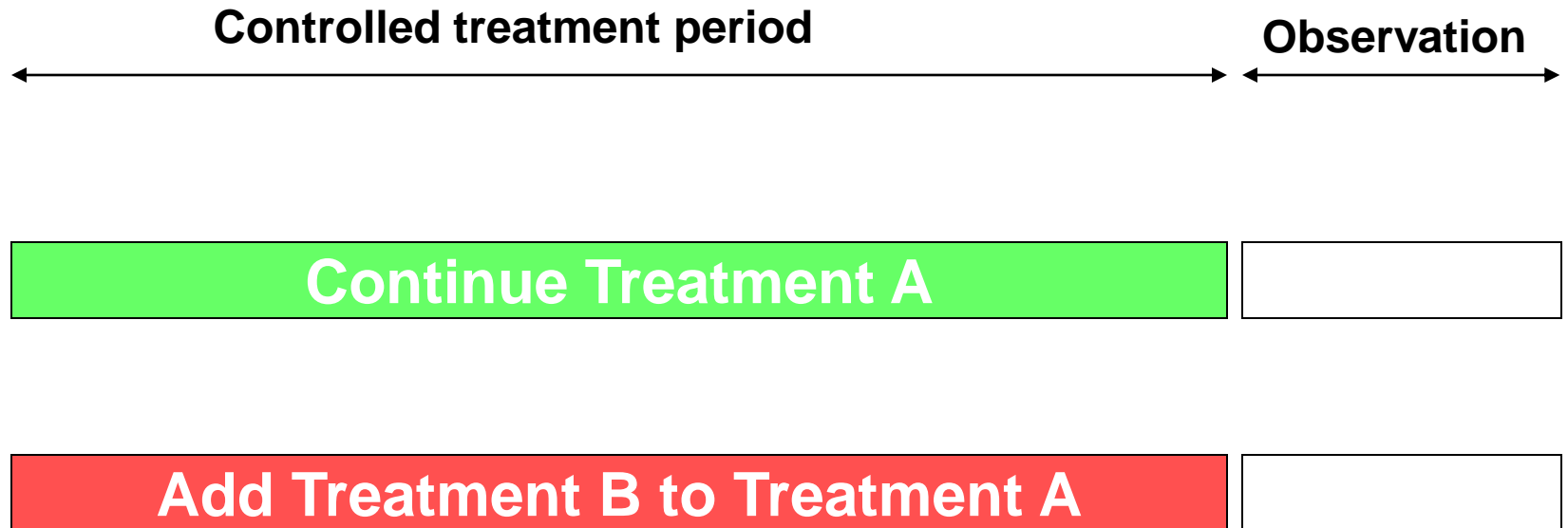
# How do we get to islet regeneration therapies?

- For monotherapy the big question will be durability
- Combination with immunotherapies will require some non-clinical studies and formal trial designs
- But, we need not wait until one or both therapies have been developed to co-develop combination therapies

# Pivotal Combination Study (prior to registration)



# Pivotal Combination Study (after drug A is registered)



# Indication for a combination therapy

**ProIlogen<sup>®</sup>**

**R<sub>x</sub>**

Combination of **BetaGen** and **IloFend<sup>®</sup>**  
**Injection**

## INDICATION

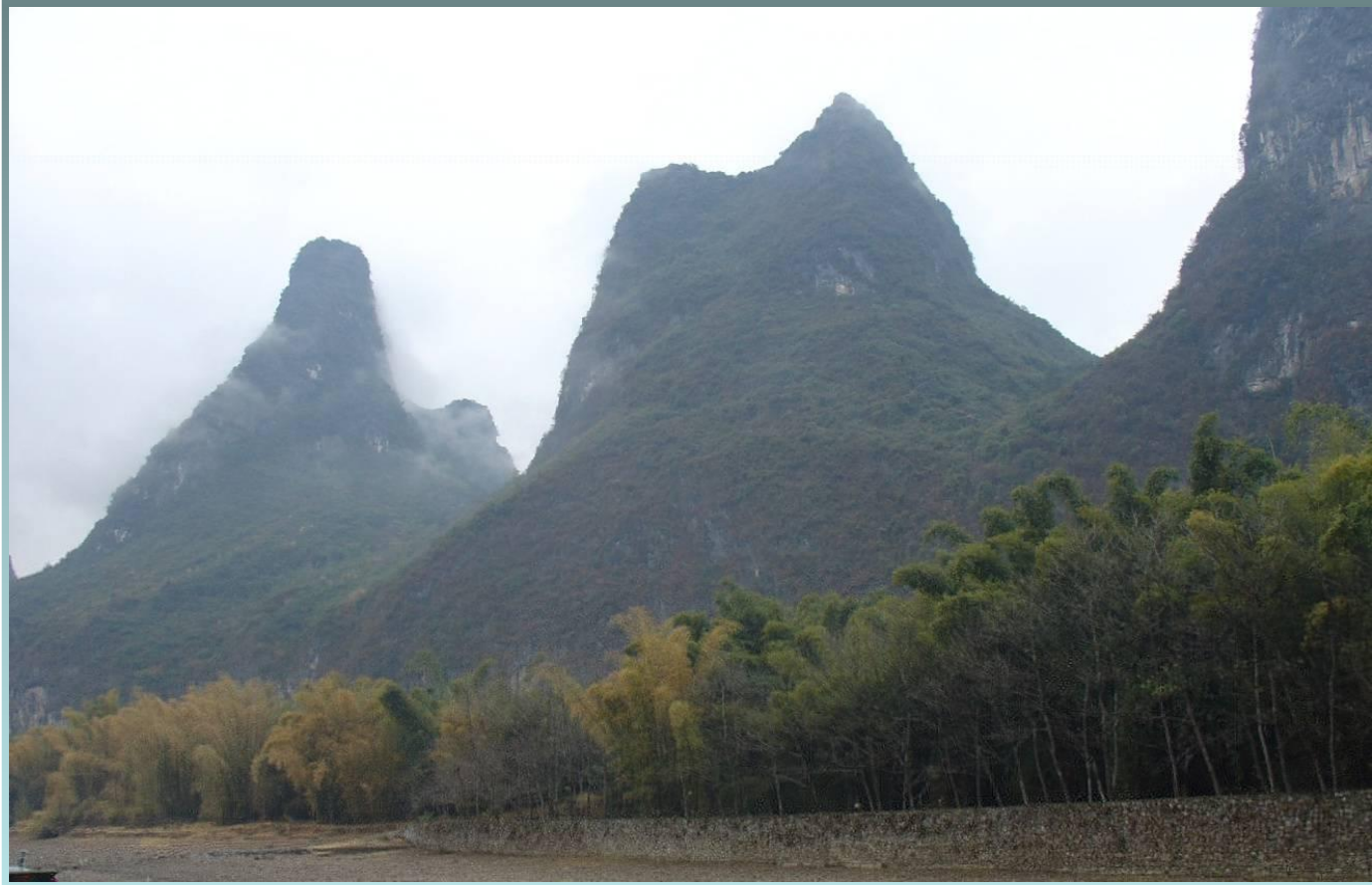
**IloFend<sup>®</sup> is indicated for the treatment and, in some cases cure, of people with type 1 diabetes mellitus.**

# For Regulatory Approval, Instead of Having to Scale a Single High Mountain....



(c) 2001 Fabio Consani

# ...A Step-Wise Approach is Needed



# **Such a Staged Approval Approach—**

- Is already provided at FDA under the regulations (Subpart H)**
- Would enable a more achievable benefit to risk relationship for initial approval**
- Reduce time and cost to market**
- Allow very large outcome studies to be done earlier and with more favorable economics**
- Would increase development of metabolic and other chronic disease therapies**

# FDA – Friend or Foe to T1DM?

