BIO 2011

The Diabetes Forum:

Emerging Strategies, Challenges, and Partnerships

June 29, 2011

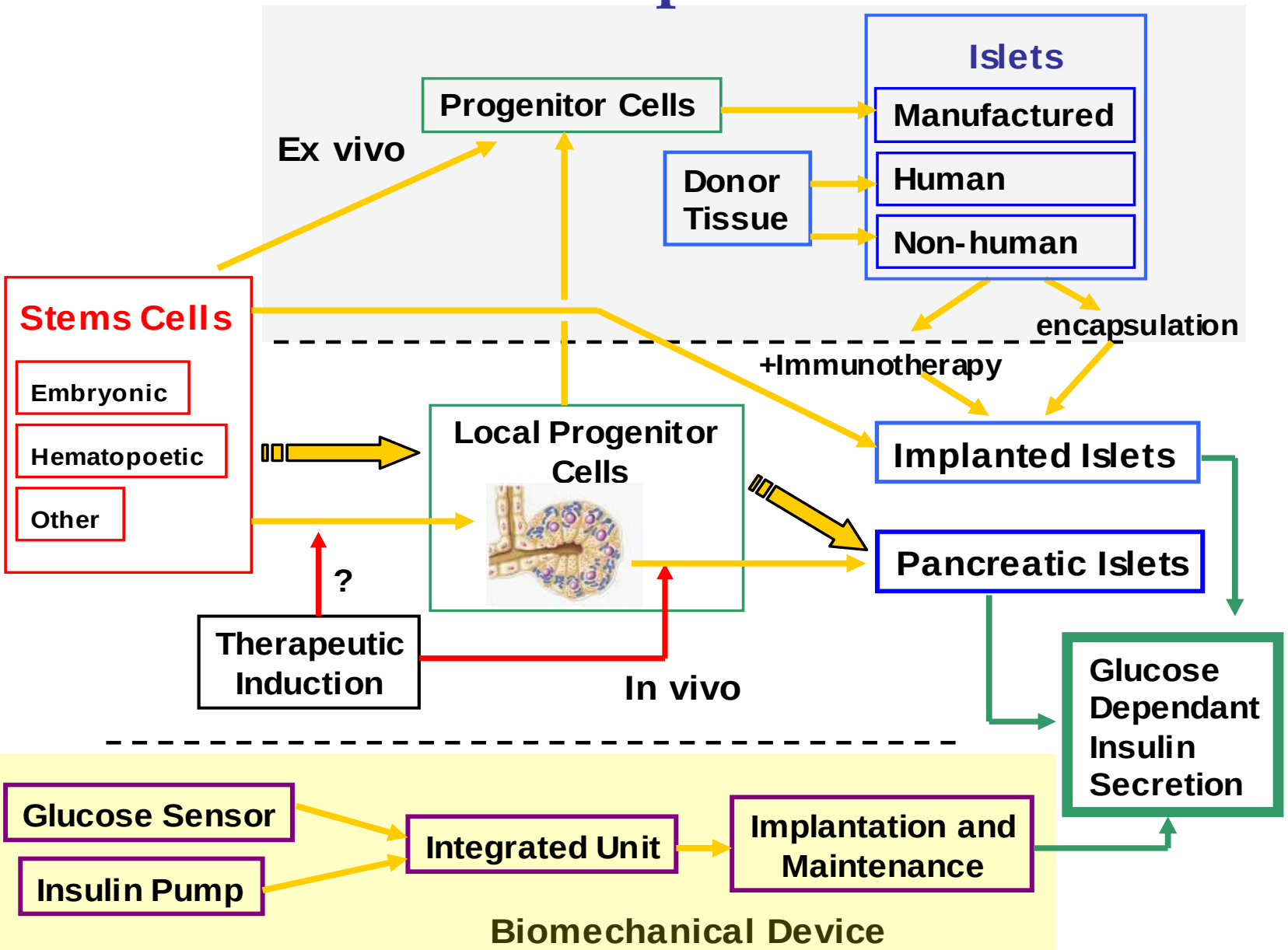
Washington, D.C.

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Draft Guidance for Industry and Food and Drug Administration Staff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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Draft Guidance for Industry and Food and Drug Administration Staff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Draft Guidance for Industry and FDA Staff: Artificial Pancreas Systems – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications

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Draft Guidance for Industry and Food and Drug Administration Staff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Draft Guidance for Industry and FDA Staff: Artificial Pancreas Systems – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications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

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

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

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.

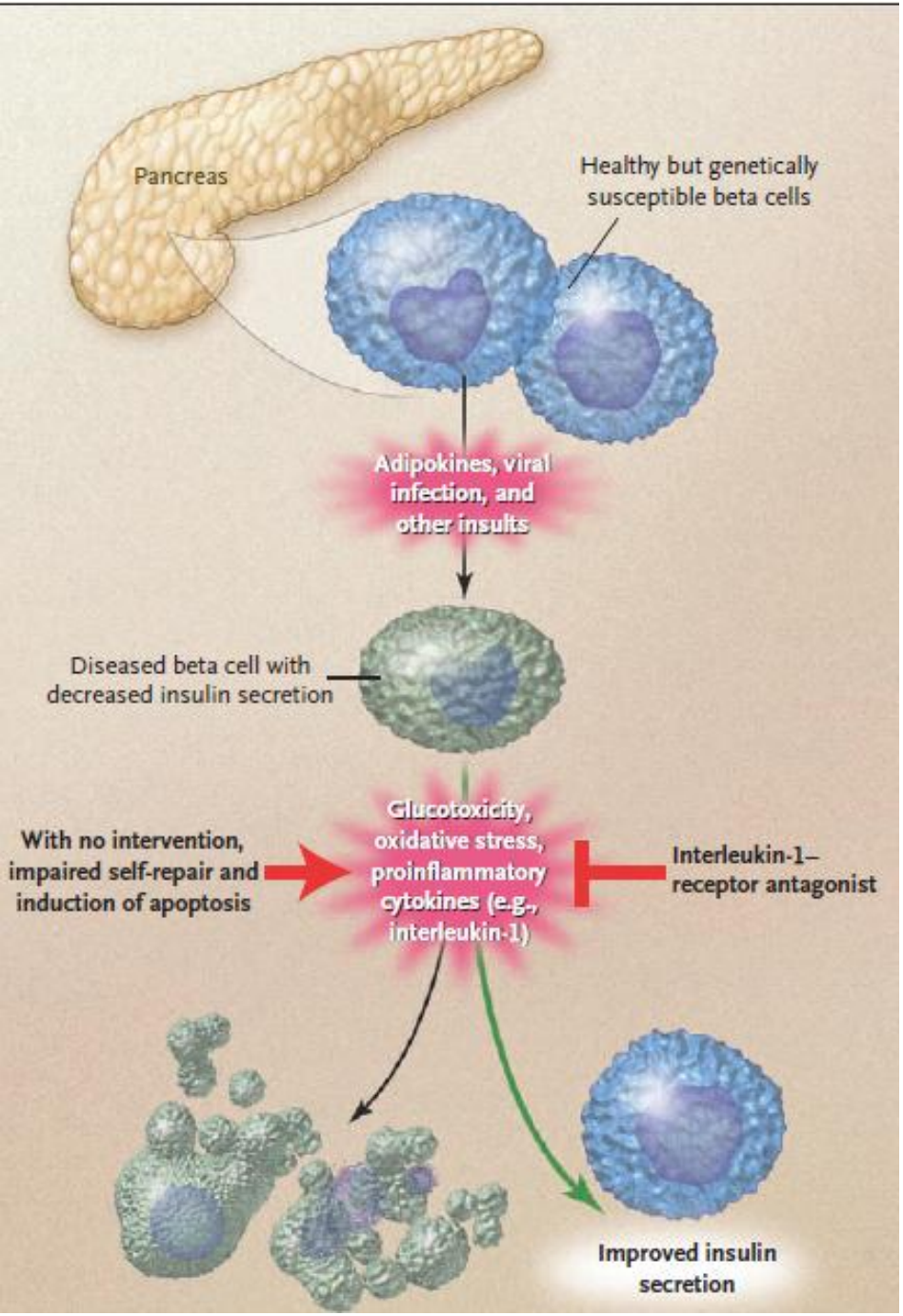
ABSTRACT

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	TIDM
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

KI Rother NEJM 356:15 2007

Why have T1DM therapies gone into Phase 3?

The goal posts are now understood.

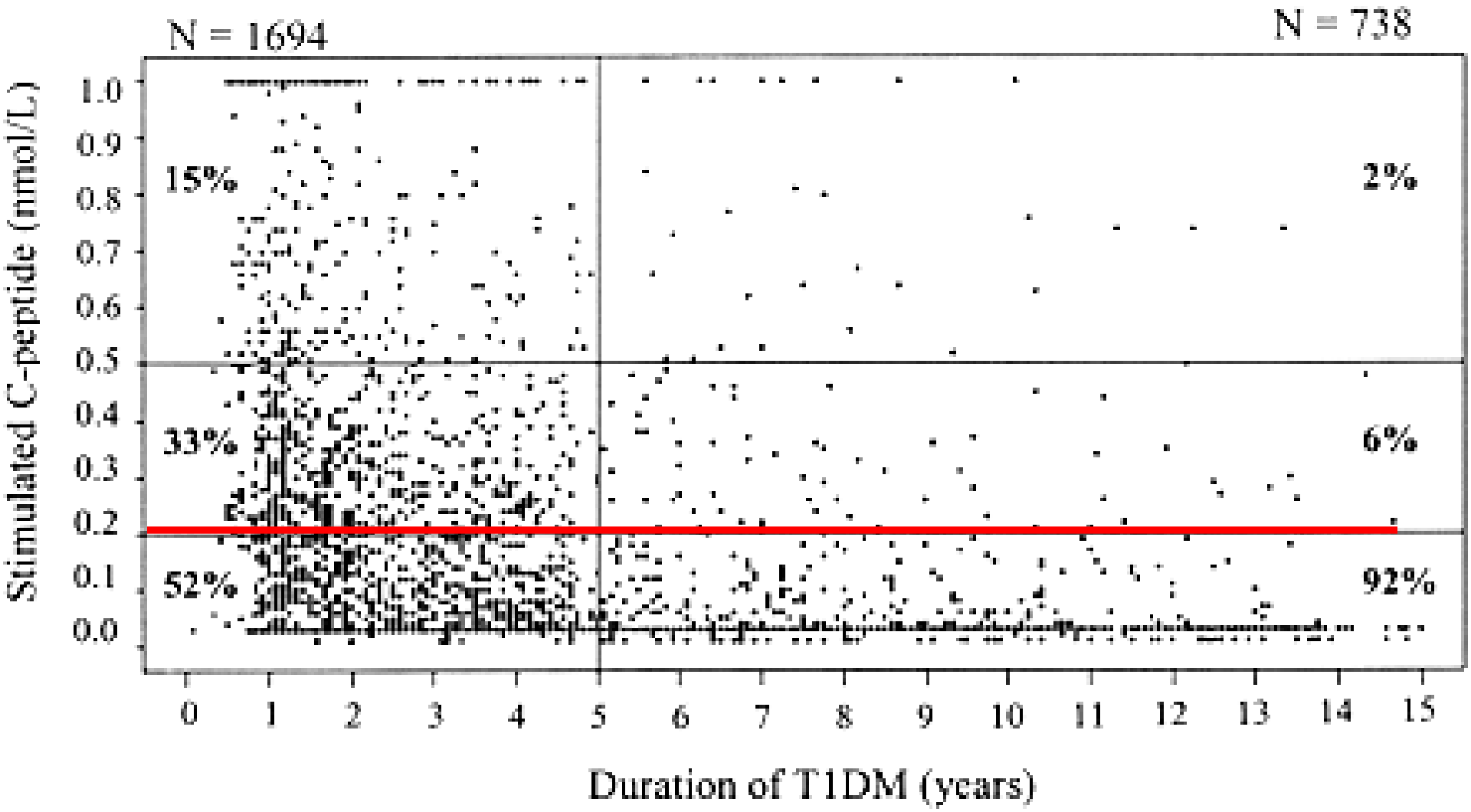
Diabetes 53:250-264, 2004

C-Peptide Is the Appropriate Outcome Measure for Type 1 Diabetes Clinical Trials to Preserve ß-Cell Function Report of an ADA Workshop, 21–22 October 2001

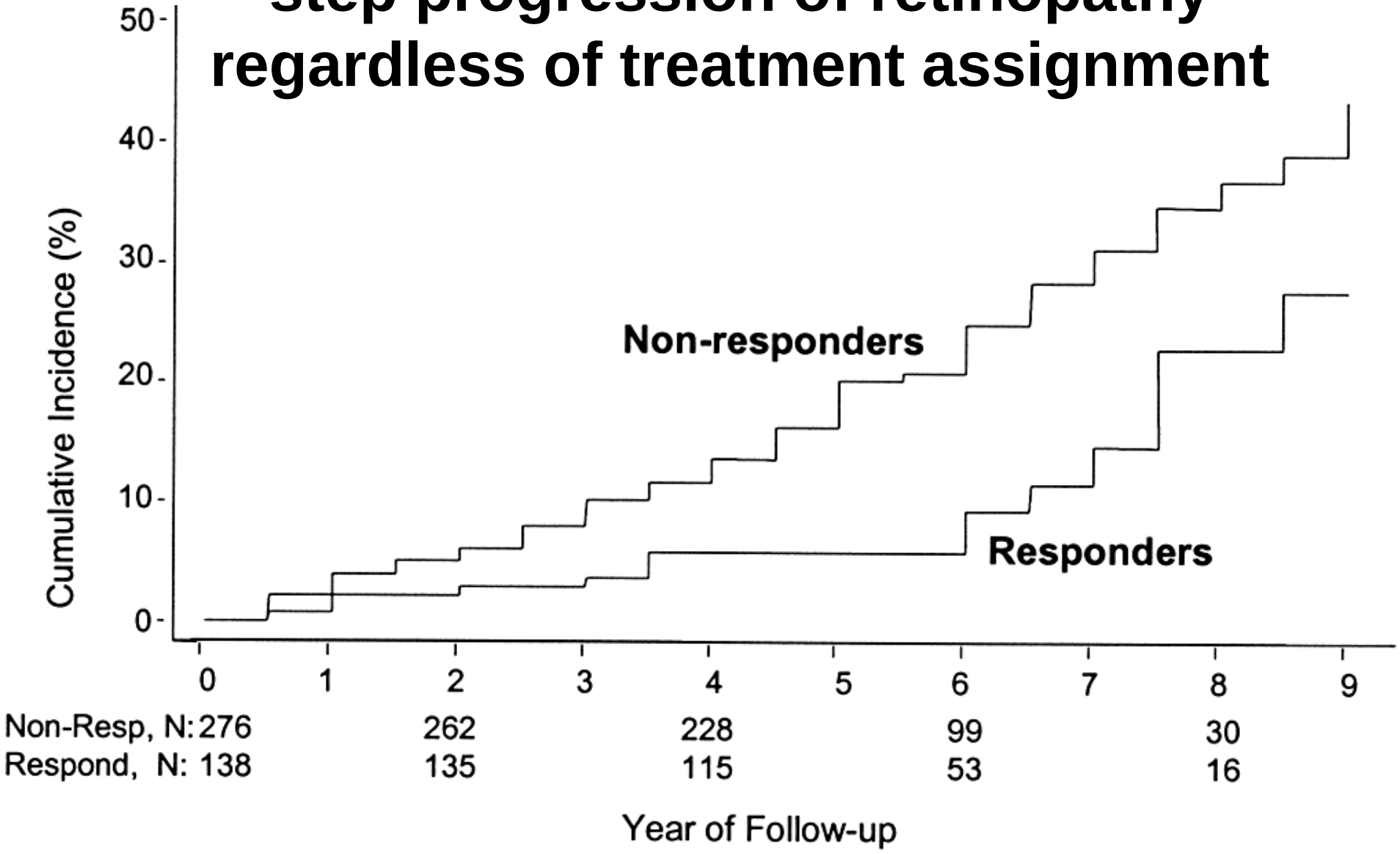
Jerry P. Palmer1,2, G. Alexander Fleming3, Carla J. Greenbaum4, Kevan C. Herold5, Lisa D. Jansa3, Hubert Kolb6, John M. Lachin7, Kenneth S. Polonsky8, Paolo Pozzilli9, Jay S. Skyler10, and Michael W. Steffes11

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® ℞

(~peptide)

Injection

INDICATION

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

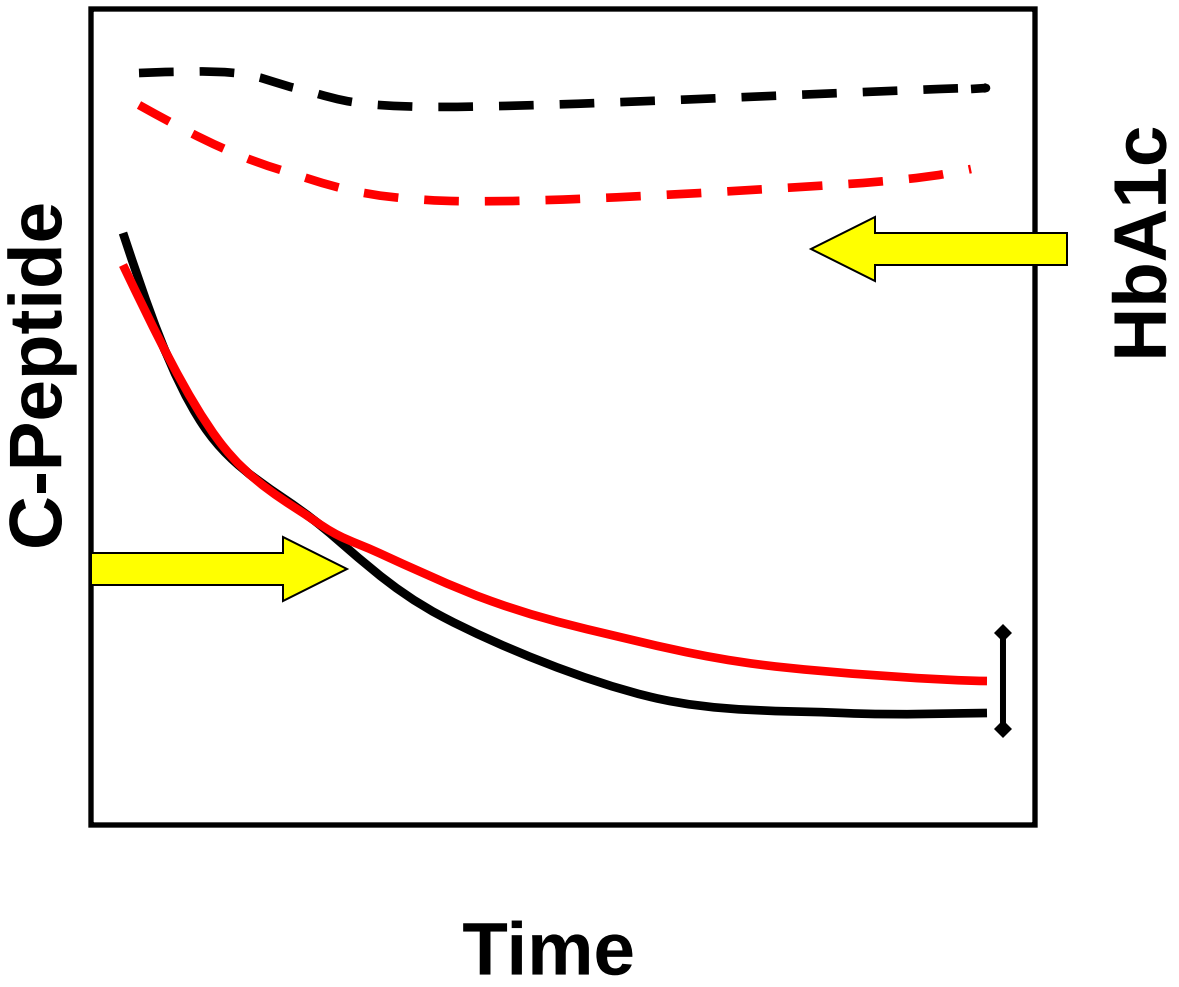
Study Design

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

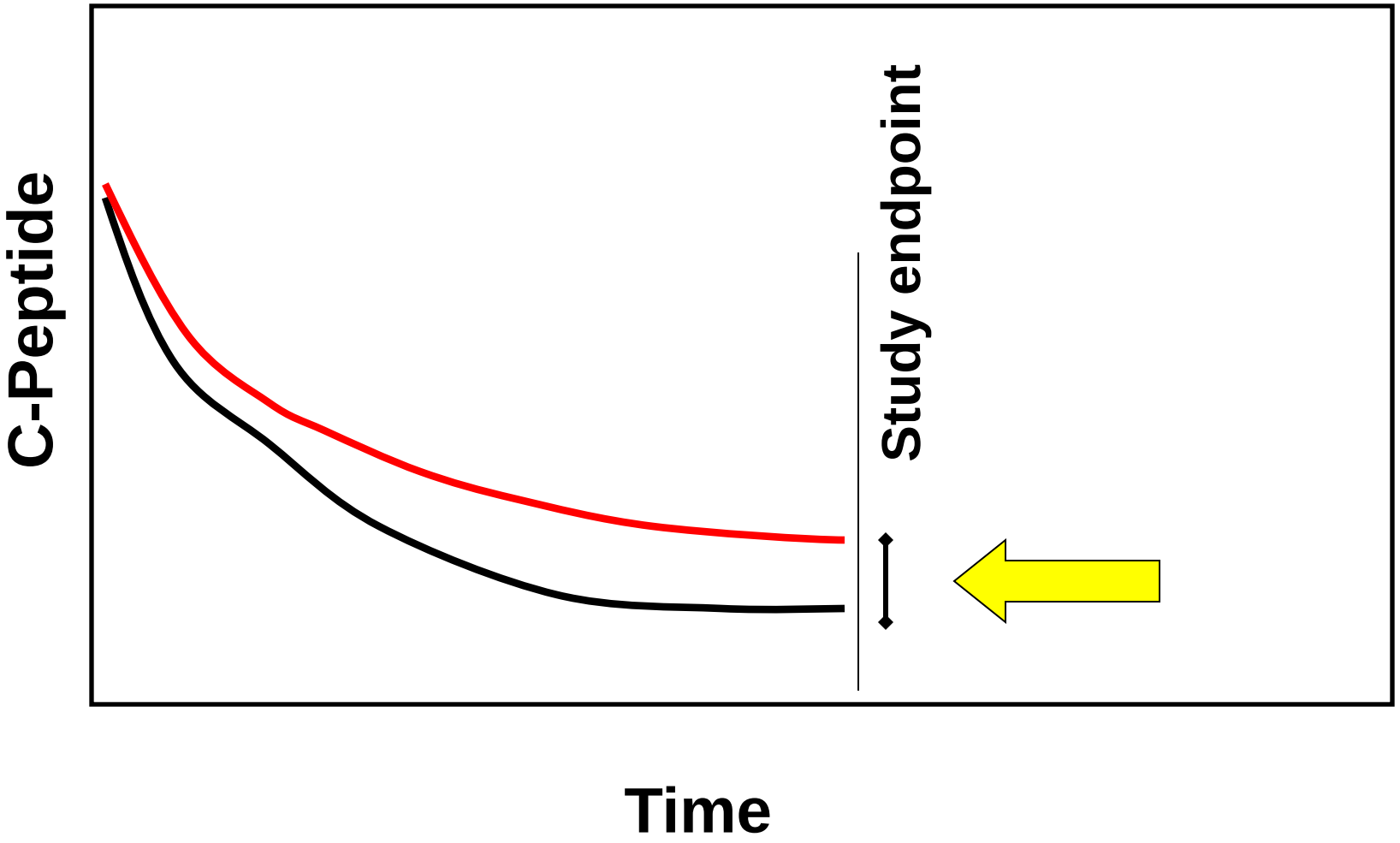
Secondary endpoints

- **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**

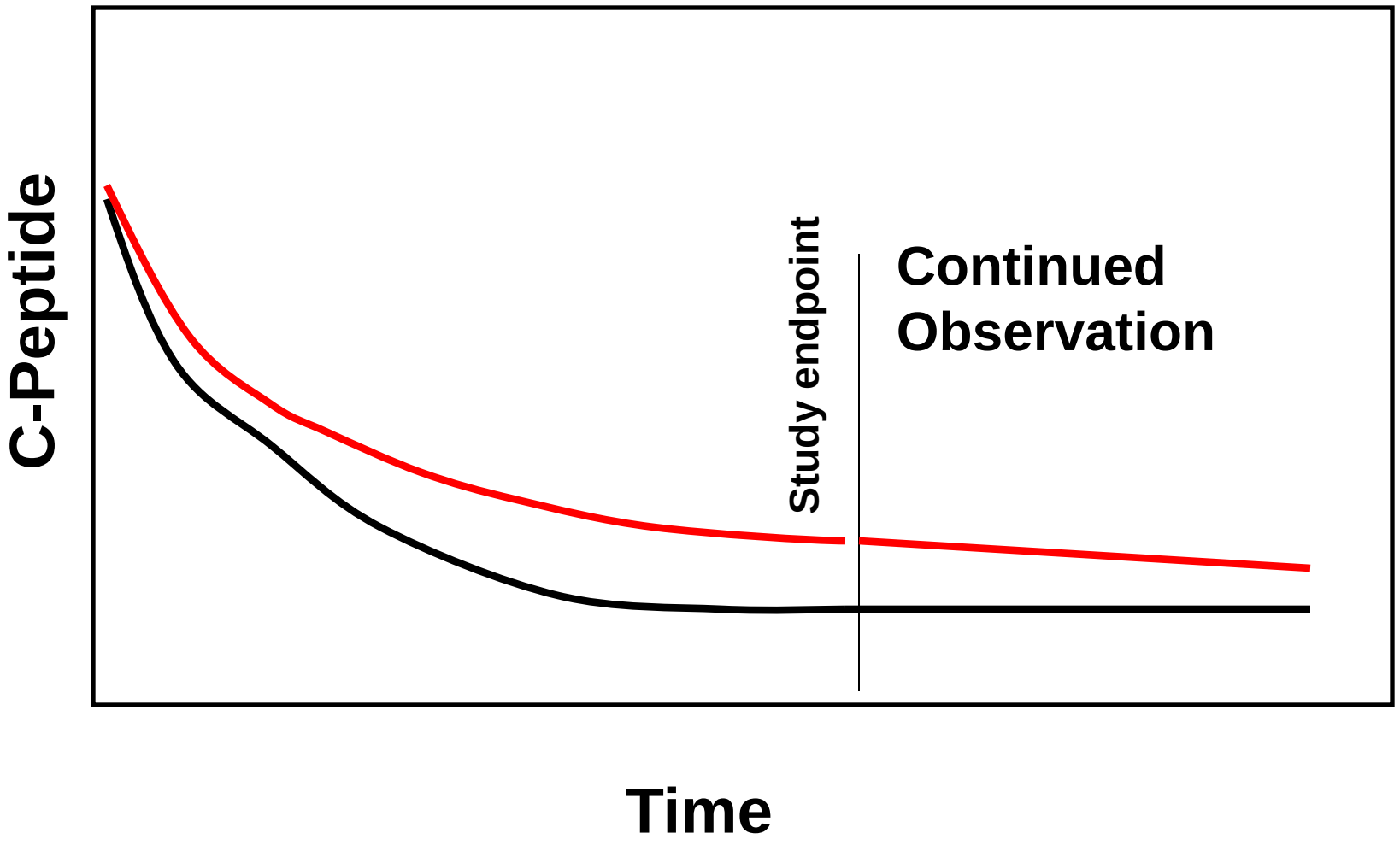
Importance of A1c as a reflection of trial integrity and not efficacy:



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 β-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® **℞**

Cryptoilotropin (peptide)

Injection

INDICATION

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

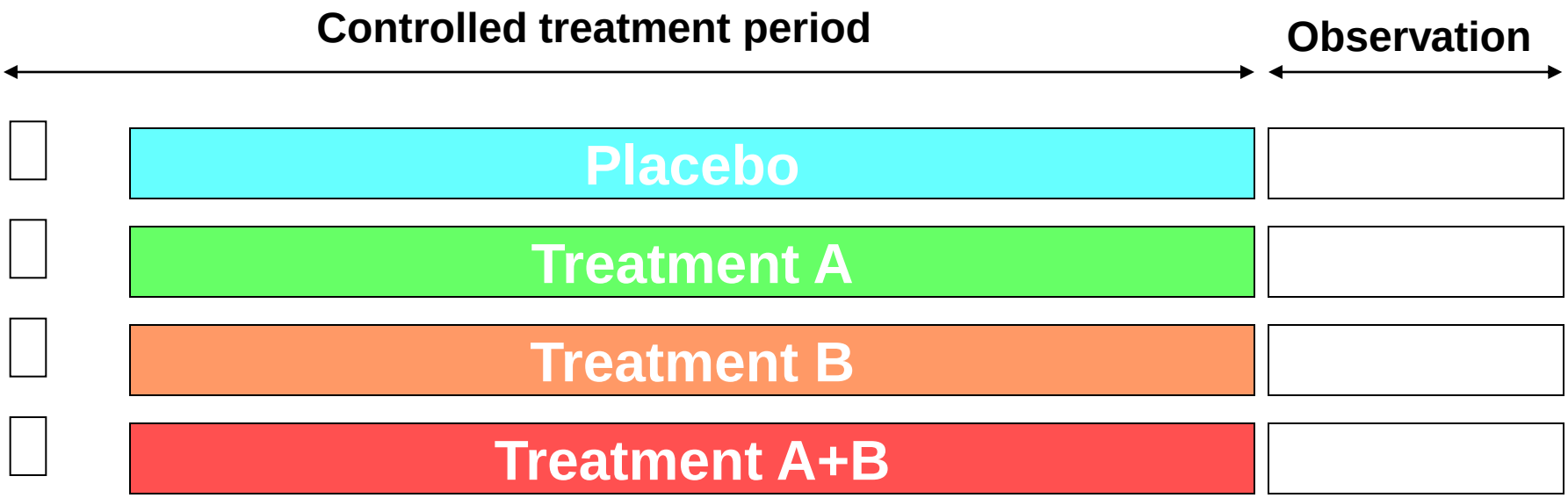
Therapies for restoring lost islet function are—

- **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**

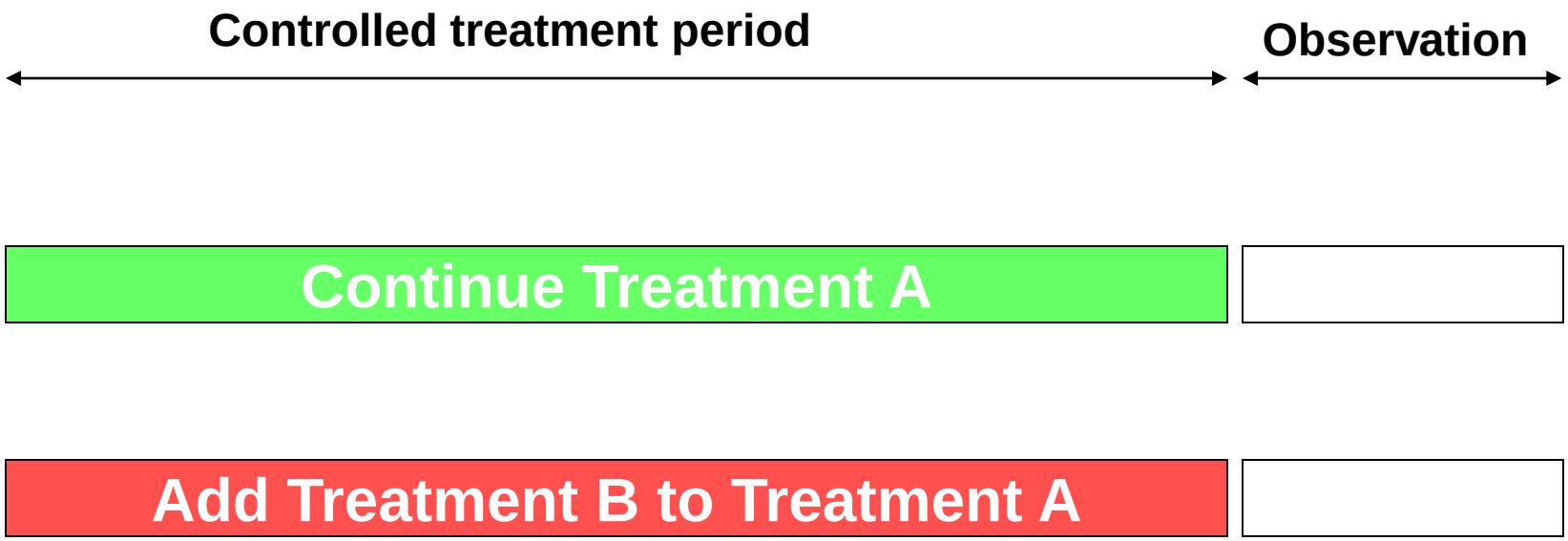
How do we get to islet regeneration therapies?

- **For monotherapy the big question will be durability**
- **Combination with immunotherapies will require some non-clinical studies and formal trial designs**
- **<u>But</u>, 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 ® ℞

Combination of **BetaGen** and **IloFend®**

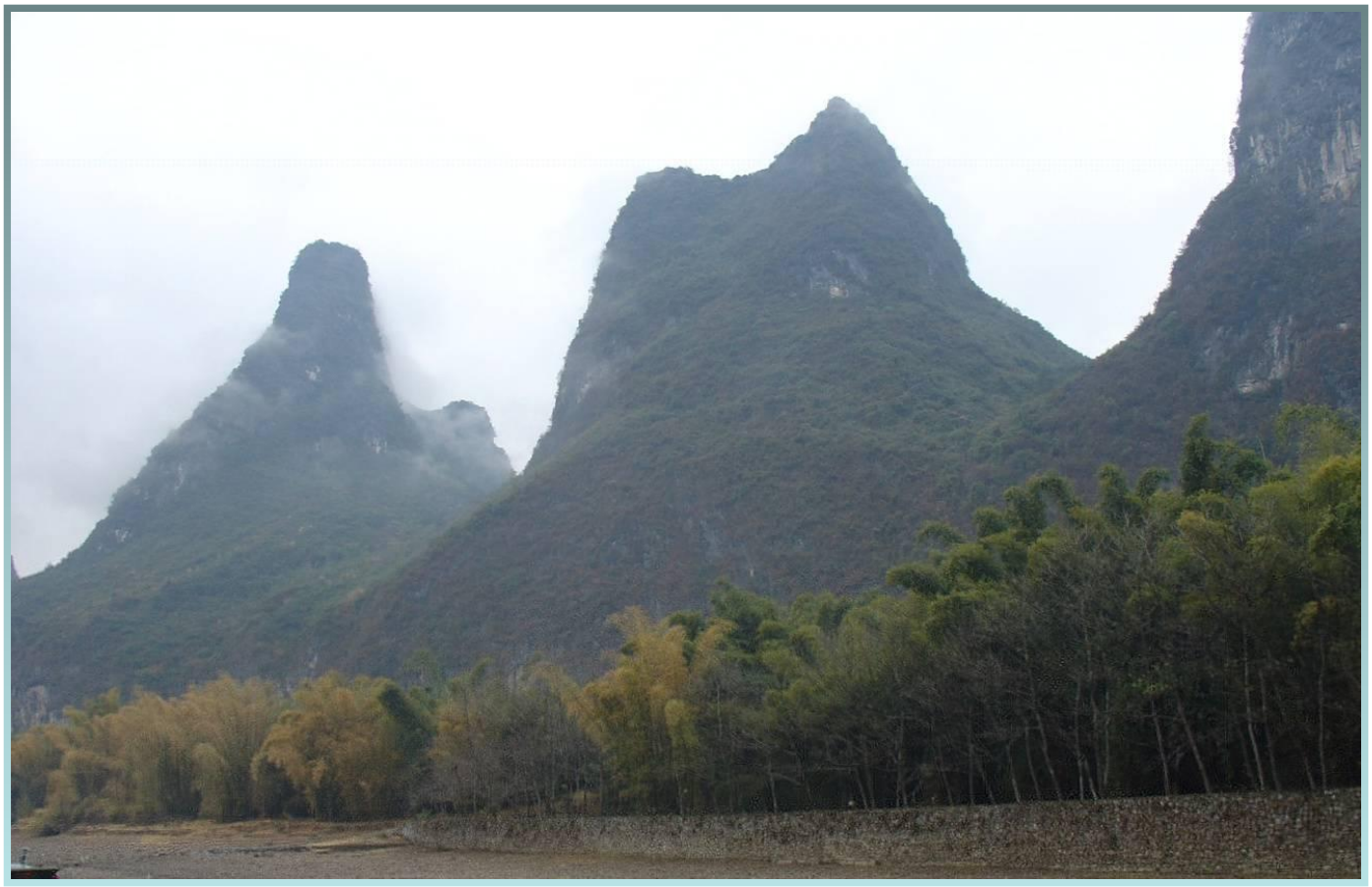
Injection

INDICATION

IloFend® 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….

…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?