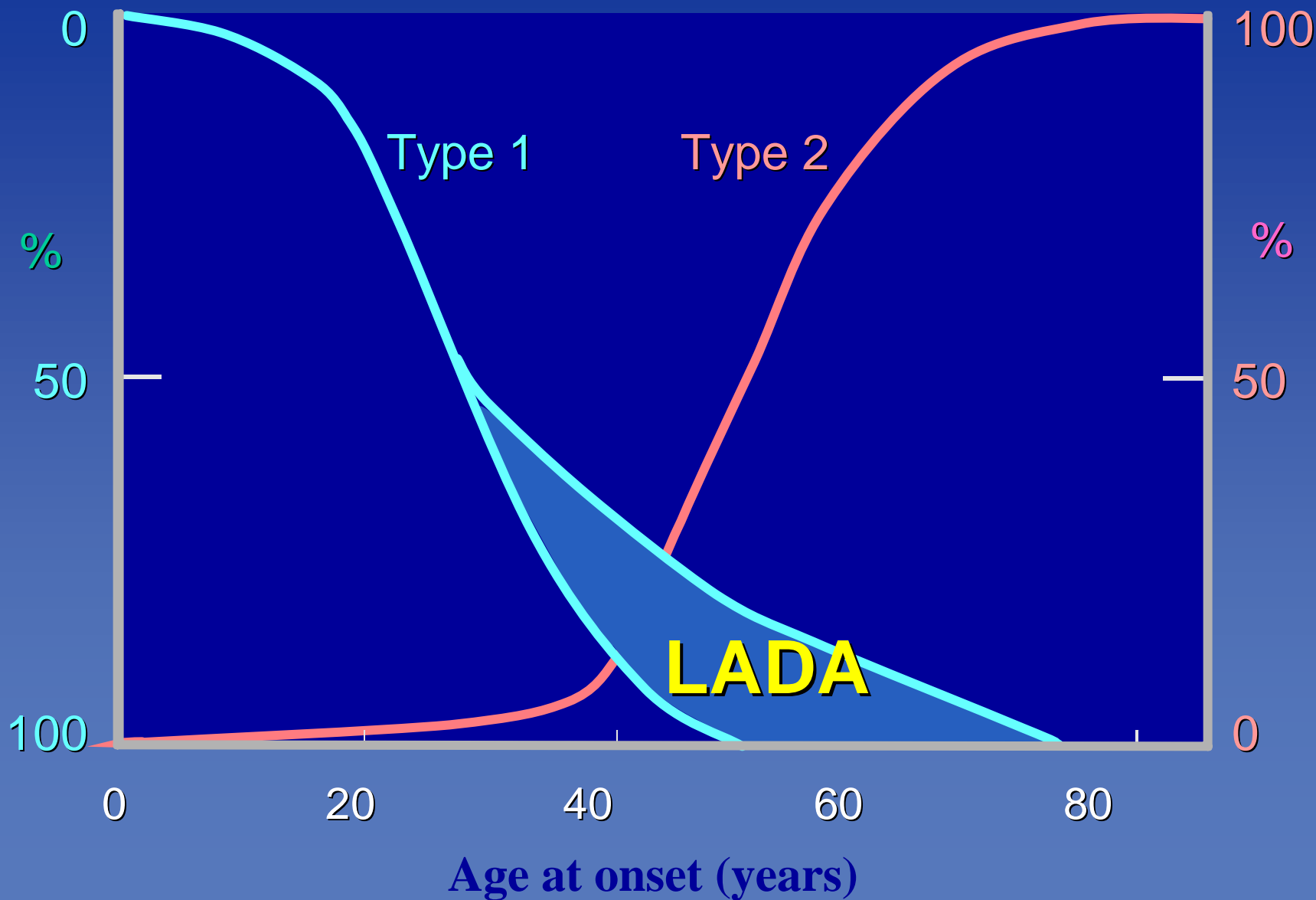
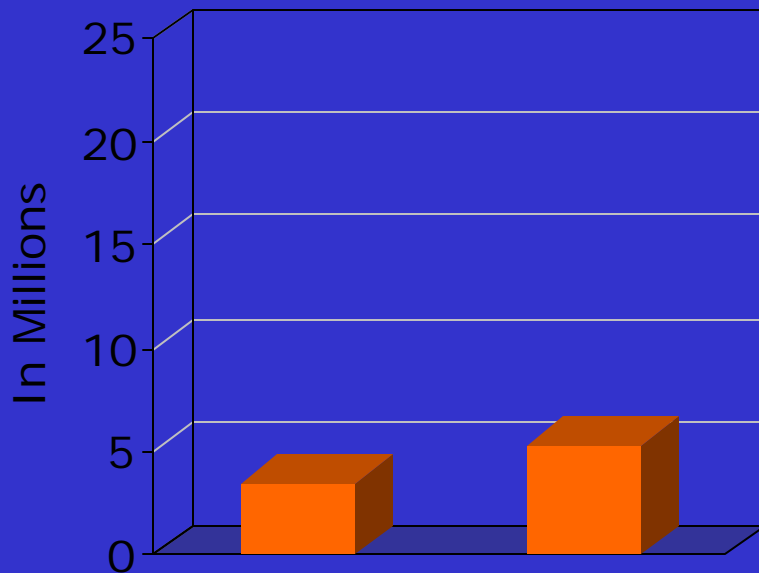


Cumulative prevalence of diabetes

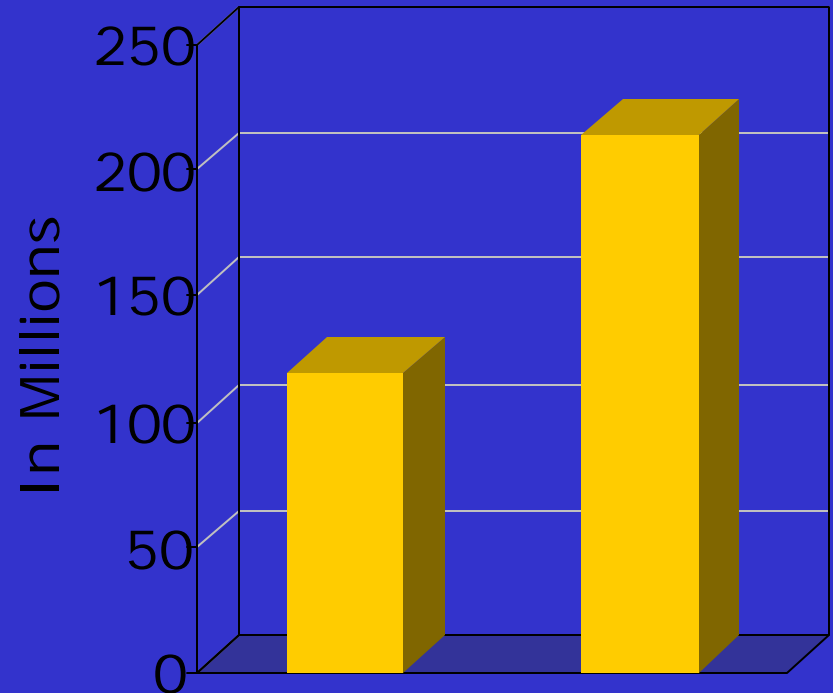


Global Estimates and Projections for Incidence of Diabetes Mellitus

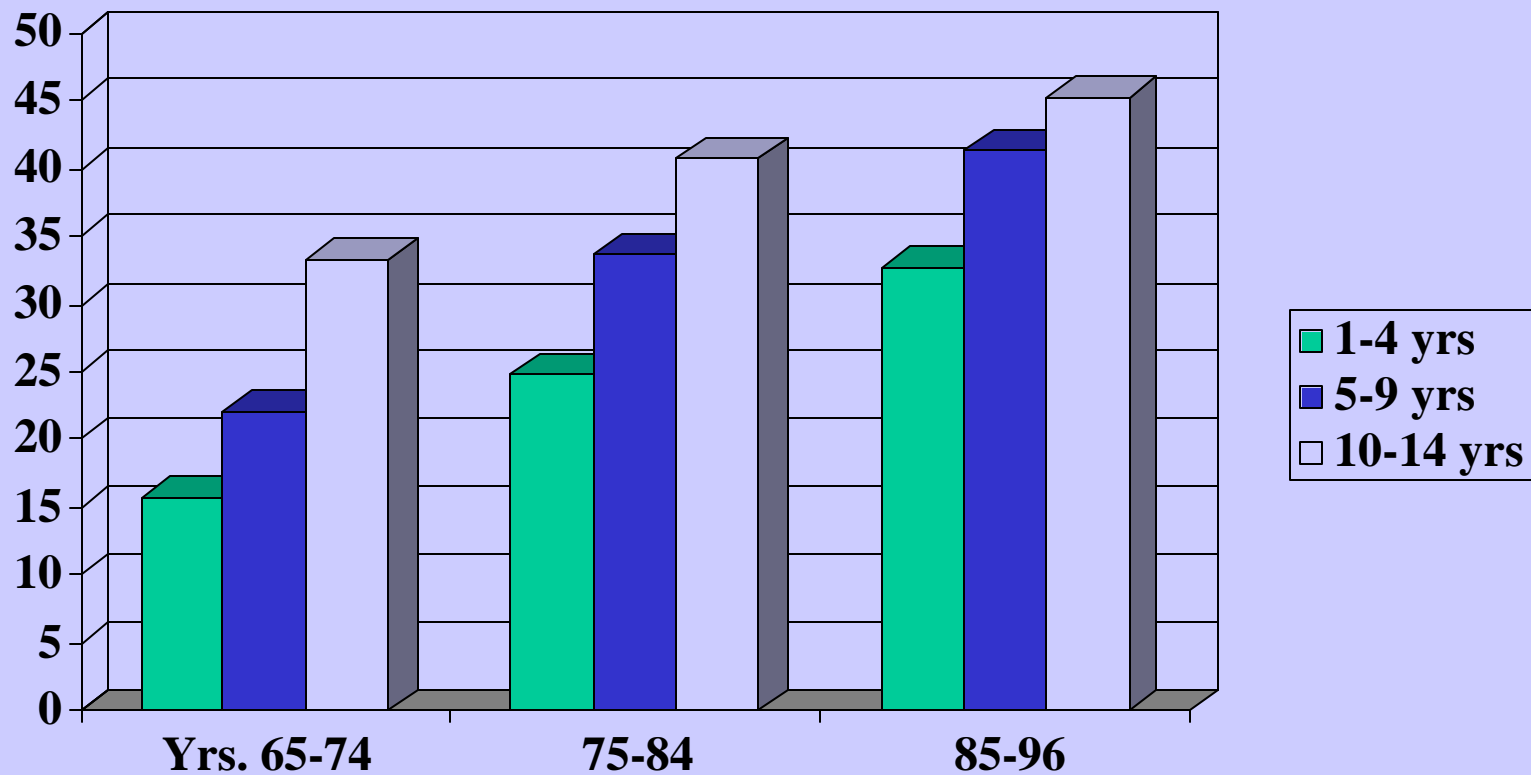
Type 1 Diabetes



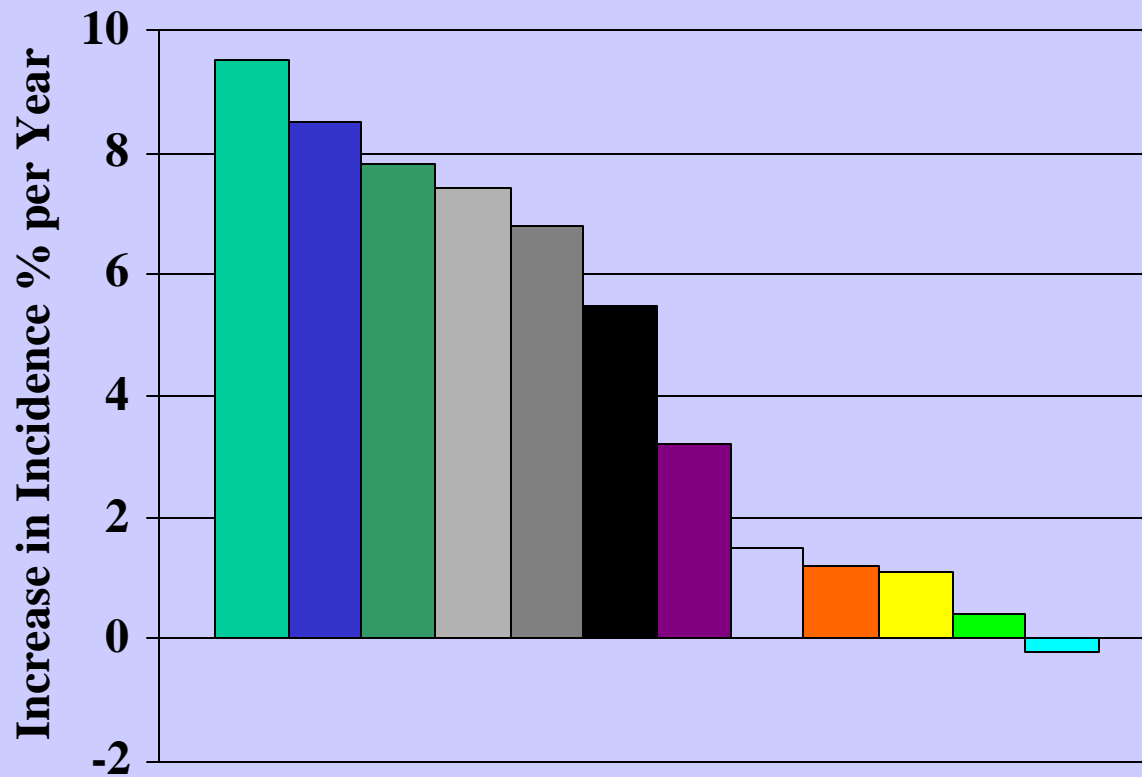
Type 2 Diabetes



Type 1 diabetes incidence in Finland 1965-96.

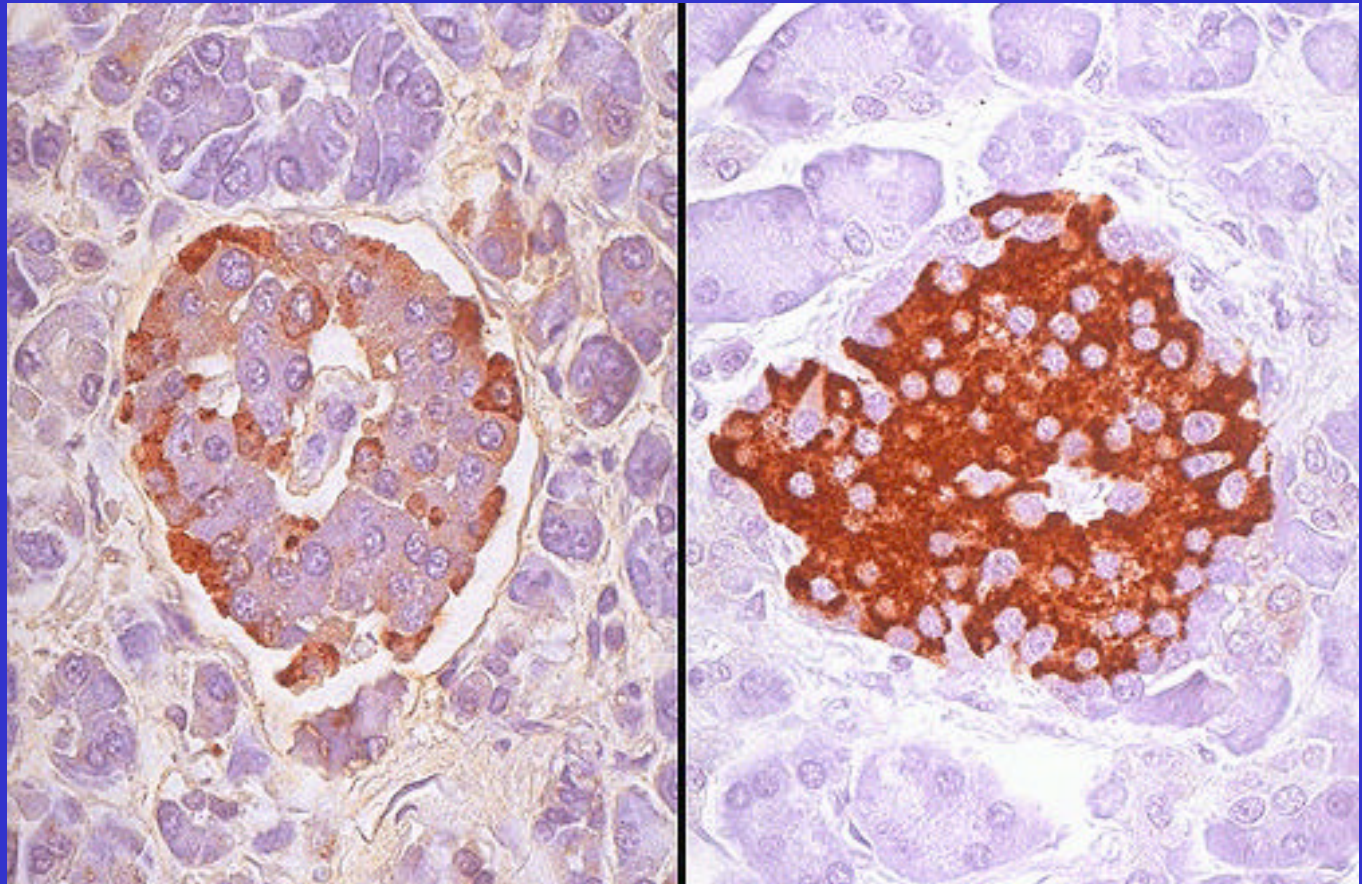


Relative Increase in Incidence of Type 1 Diabetes in Children < 14 Years

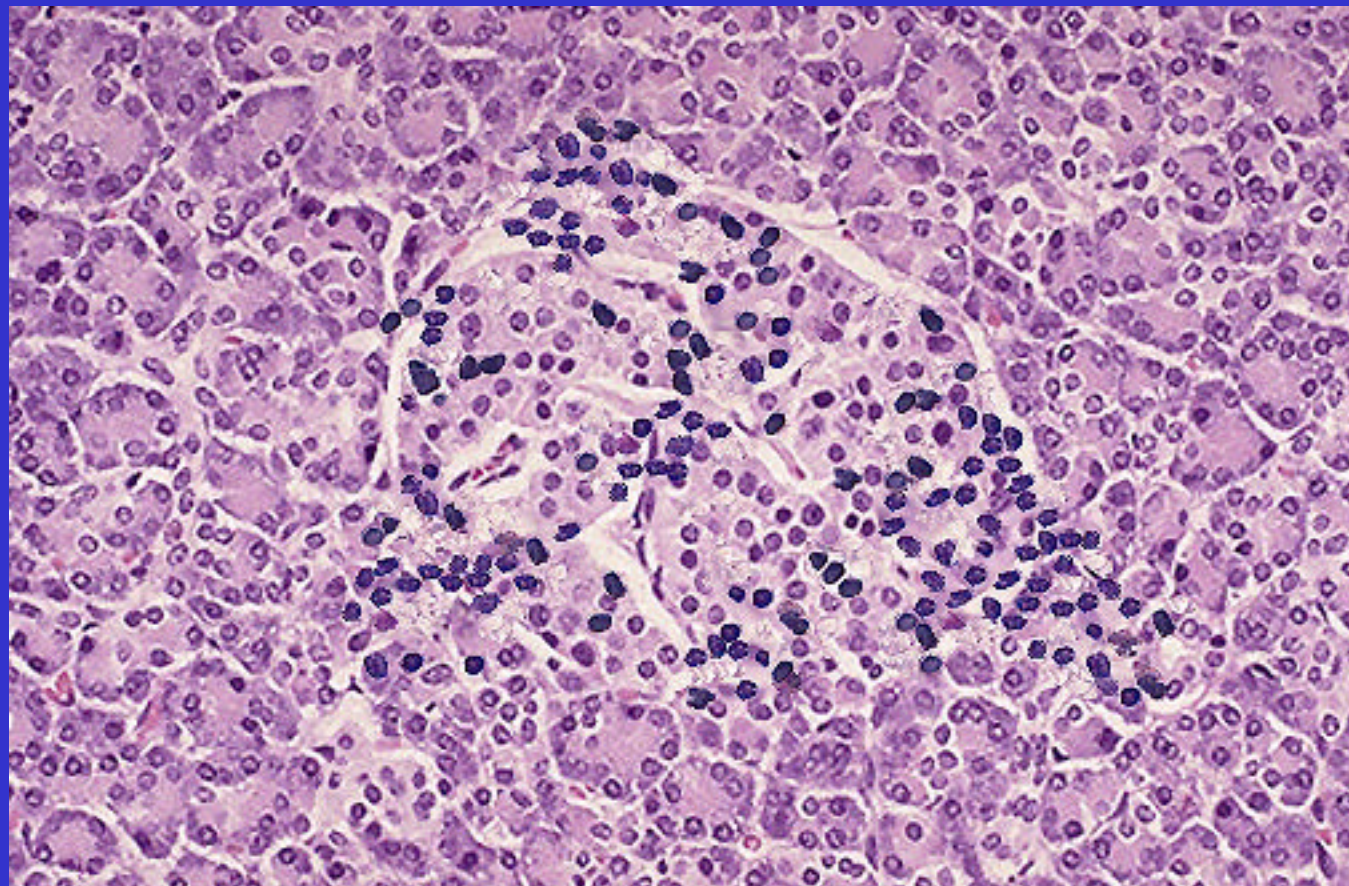


Change globally: 2.5 % per year (2.32-2.66)

Normal islets



Insulinitis



Type 1 Susceptibility Genes

HLA-DQ (6p)

Insulin-gene VNTR (11p)

CTLA-4 (2q)

Many others proposed

Pathogenesis

Markers of b-cell autoimmunity:

Insulin autoantibodies (IAA)

GAD65 autoantibodies (GAD65Ab; GADA)

I-A2/IA-2 β autoantibodies (IA-2Ab)

Diagnostic sensitivity and specificity of autoantibodies for Type 1 diabetes

Autoantigen	Sensitivity	Specificity
Insulin	40-70%	99%
GAD65	70-80%	99%
IA-2	50-70%	99%

Genetic and age-related factors affect the risk for type 1 diabetes.

Autoantigen	Association to HLA-DQ	Association to INS VNTR	Association to age
Insulin Ab	DQ8	yes	young more frequent
GAD65Ab	DQ2	no	little effect of age
IA-2/IA-2Ab	DQ8	no	young more frequent

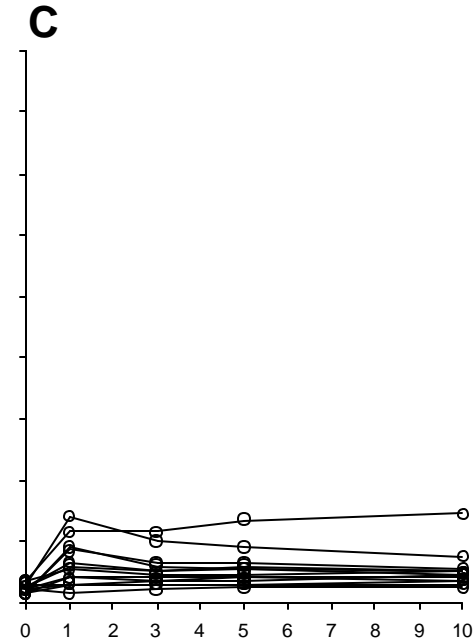
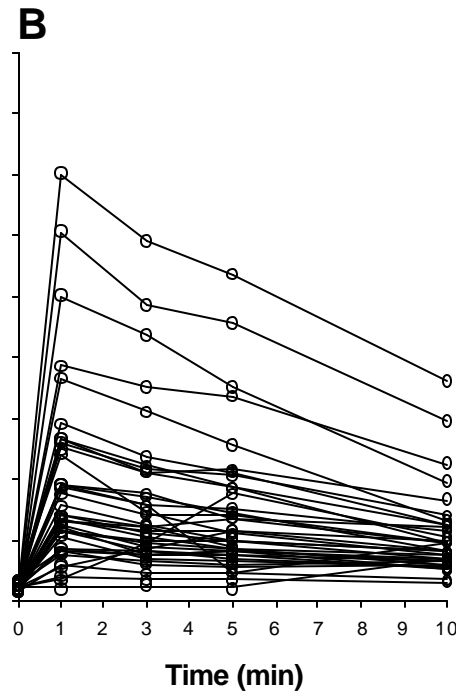
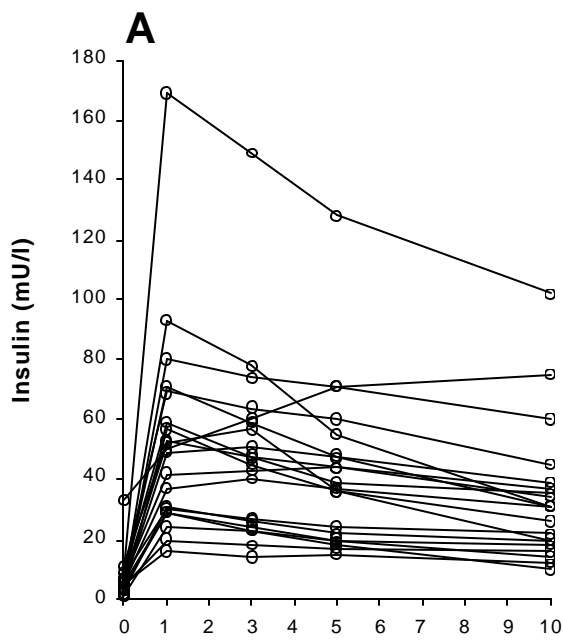
Residual β -cell function in new onset Type 1 diabetes

Age (years)	C-peptide level within normal range		
	At diagnosis	One year	Two years
0-15	20%	10%	<5%
15-34	60%	55%	46%

Sensitivity, specificity and positive and negative predictive values for classification of type 1 diabetes in type 2 diabetes patients followed for three years.

	Sensitivity (%)	Specificity (%)	Positive predictive	Negative predictive
fCP below reference Interval (<0.25 nmol/l)	53	96	82	87
GAD65 Ab present	81	91	85	88
GAD65Ab present and fCP <0.25 nmol/l	32	100	100	70

fCP is fasting C-peptide



ICA neg

positive

positive

T1DM no

no

yes

Children 1-5 years of age

Keskinen et al. Diabetologia 45:1639-48, 2002

In summary.....

Initiators

- *virus?*
- *diet?*

Promoters

- *genes?*
- *virus?*
- *diet ?*

**Genetic
susceptibility**



Autoimmunity



**Clinical
diabetes**



WHAT CONDITION TO TREAT?

Types of Interventions: Type 1 Diabetes Prevention Trials

Type	Example
Antigen-base therapy	insulin, heat shock peptides, GAD65
Immunosuppressive	cyclosporin, azathioprine, prednisone
Immunostimulaton/modulation	BCG, anti-CD3, nicotinamide, Vitamine D
Beta cell rest	insulin, diazoxide, octreotide

Treatment of marker positive subjects.

- **Diabetes Prevention Study-1 (DPT-1). No effect.**
 - **Effects of insulin in relatives of patients with type 1 diabetes mellitus.**
N Engl J Med. 346:1685-91, 2002 .
- **ENDIT. No effect.**
 - **Gale EA, et al and the European Nicotinamide Diabetes Intervention Trial (ENDIT) Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes.**
Lancet 363:925-31, 2004.
- **Type 1 Diabetes Prediction and Prevention Project (DIPP).**
 - **Nasal insulin in children at risk - ongoing.**
- **Trial to Reduce IDDM in the Genetically at Risk (TRIGR).**
 - **Breast feeding plus a) breastfeeding supplements of a trial formula based on extensively hydrolyzed protein;**
 - **b) a special trial formula containing a smaller amount of hydrolyzed protein.**

PAST RESULTS

“Positive” Primary Outcome:

Azathioprine

Azathioprine/steroids

Cyclosporin

DiaPepp

Linomide

Negative Primary Outcome:

Nicotinamide

Insulin

Methotrexate

Anti-CD4

Antioxidants

BCG

Treatment of newly diagnosed T1DM.

- **Human Insulin B-chain in IFA. Phase I; ITN; Orban, USA**
- **Daclizumab (DZB). Open; Roche Rodriguez, USA**
 - **Prevention of Diabetes Progression (PDPT)**
- **MMF+DZB. Phase I/II, TrialNet; Gottlieb, USA**
- **Oral Interferon alpha. Phase II; NIDDK Brod, USA**
- **NBI 6024 (insulin like analogue): Phase I/II; Neurocrine; Gottlieb, USA**
- **HOKT3 gamma 1(ala-ala): Phase II; ITN; Herold, USA**

hOKT3 gamma 1 (Ala-Ala)

- * Treatment with the monoclonal antibody:
maintained or improved insulin production after one year in
9/12 patients compared to 2/12 controls (P=0.01).
- *The treatment effect on insulin responses lasted for at least
12 months after diagnosis.
- *HbA1c levels and insulin doses were also reduced.
- *No severe side effects occurred, and the most common
side effects were fever, rash, and anemia.
- *Clinical responses were associated with a change in the ratio of
CD4+ T cells to CD8+ T cells T 30 and 90 days.

Herold et al: N Engl J Med. 346:1692-8, 2002 .

**Safety, Tolerability, Immunological and Clinical Efficacy of
Multiple Subcutaneous Doses of AVE0277 in Latent
Autoimmune Diabetes in Adults (LADA)**

Phase II trial sponsor: Aventis

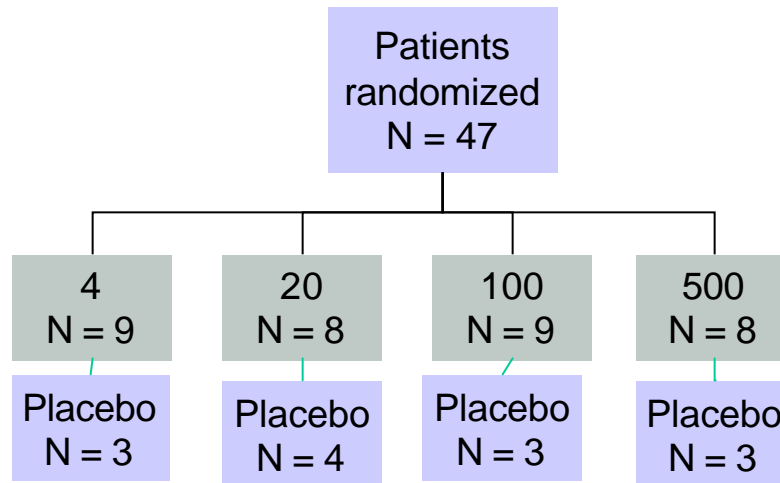
**Diagnosis of diabetes mellitus by WHO classification:
more than 2 months and less than 5 years duration;
controlled by diet and insulin (plus metformin if needed)
for 2 or more weeks prior to the baseline visit.**

Age 30 to 55 years.

**Subjects will be screened for GAD65 autoantibodies and C-
peptide (n= 100)**

A phase II randomized, double blind, placebo controlled trial in LADA patients.

- Following a screening phase, 47 LADA patients were randomized into four dose groups:
- 4, 20, 100, 500 μg
- injected twice - subcutaneously - four weeks apart.



AIMS: safety and impact on diabetes and immune parameters:

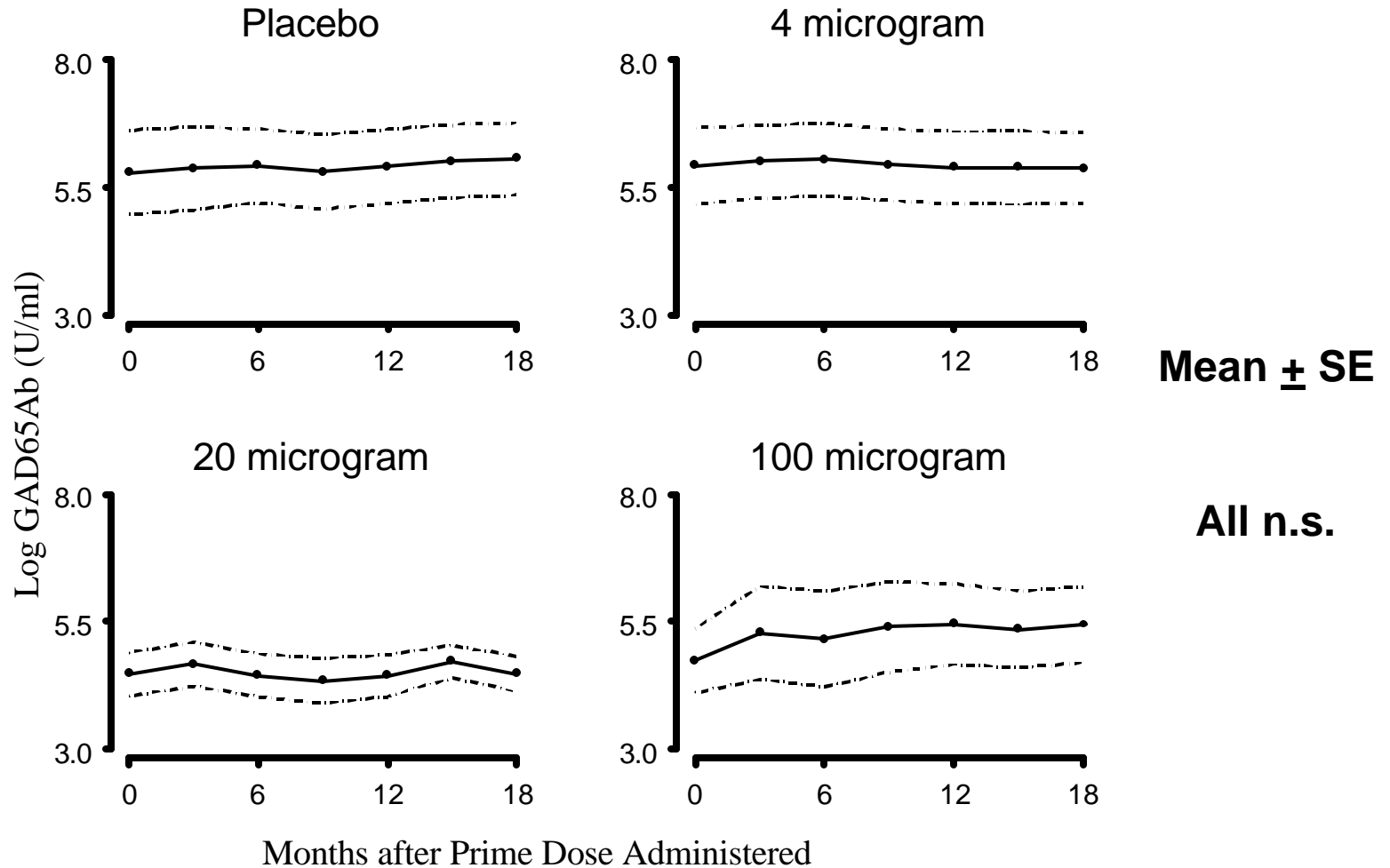
- Adverse events
- GAD65Ab levels
- c-peptide levels
- HbA1c
- T cell subsets

**Lost to follow-up
(3/47).**

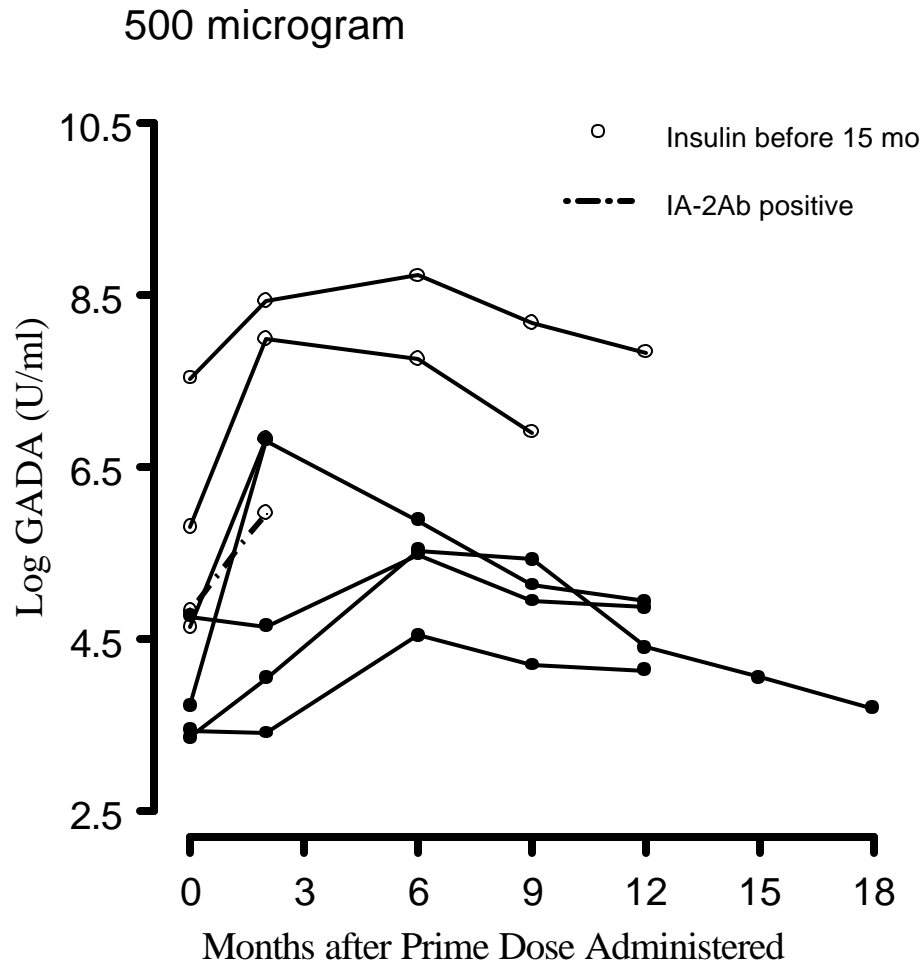
Microgram	Patients Remaining in Study							Reason
	0	3	6	9	12	15	18	
Placebo	13	13	13	12	12	12	12	Personal
4	9	9	9	9	8	8	8	Personal
20	8	8	8	8	8	8	8	Personal
100	9	9	8	8	8	8	8	
500	8	8	8	8	8	8	-	

**NO
STUDY-RELATED
ADVERSE EVENTS
IN THE REMAINING
44 PATIENTS.**

No effects on GAD65Ab levels in the placebo, 4, 20, and 100 μ g dose groups.



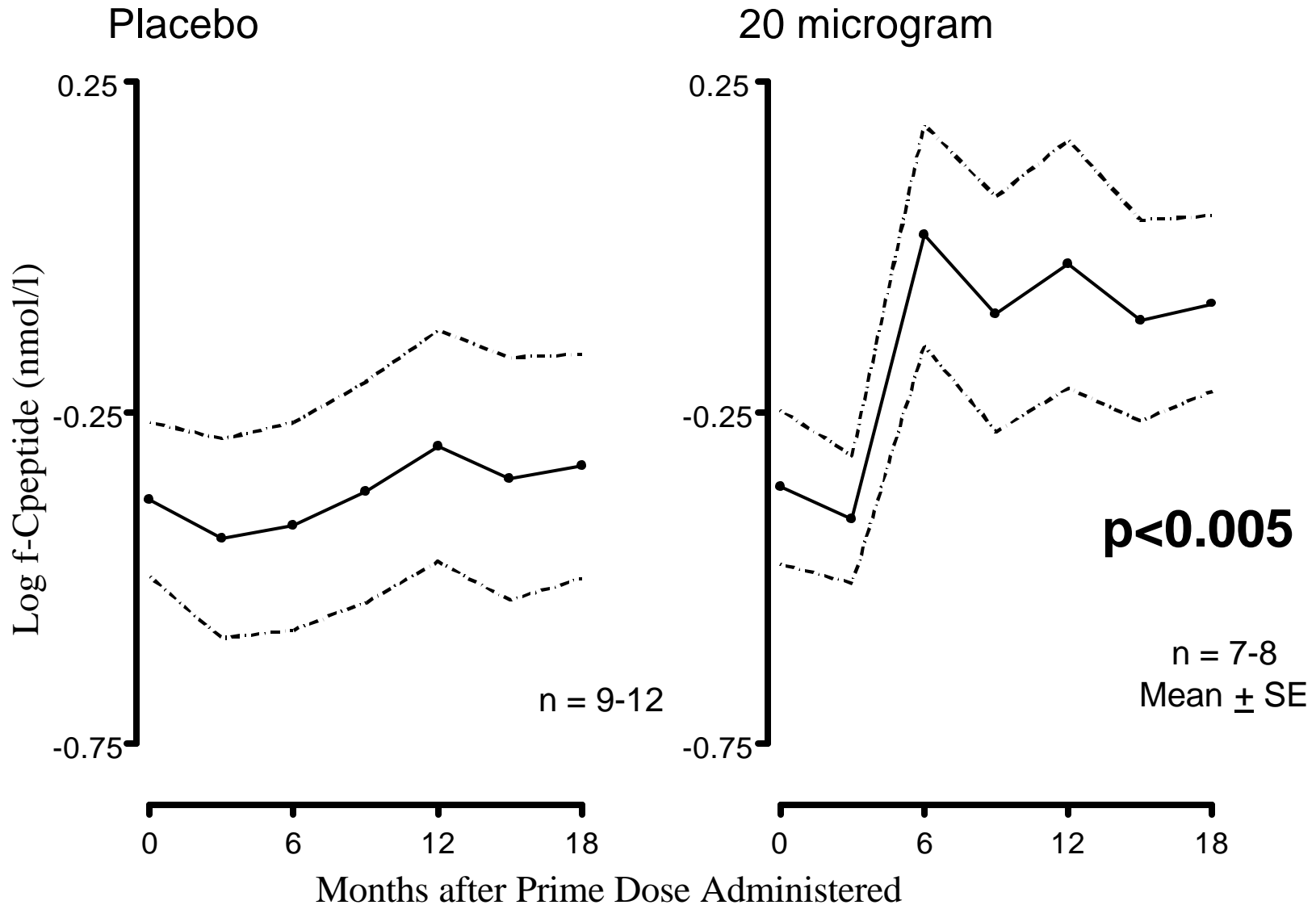
Transient increase in GAD65Ab levels in the 500 μ g dose group.



Patients remaining insulin free.

Microgram	Patients without insulin treatment.							Lost
Placebo	12	12	11	11	11	9	9	3/12 (25%)
4	8	8	8	6	5	4	4	4/8 (50%)
20	8	8	8	7	7	7	7	1/8 (13%)
100	8	8	7	7	7	7	7	1/8 (13%)
500	8	8	6	6	5	4	-	4/8 (50%)
	0	3	6	9	12	15	18	
	Months after first injection							

C-peptide increased in the 20 mg dose group.

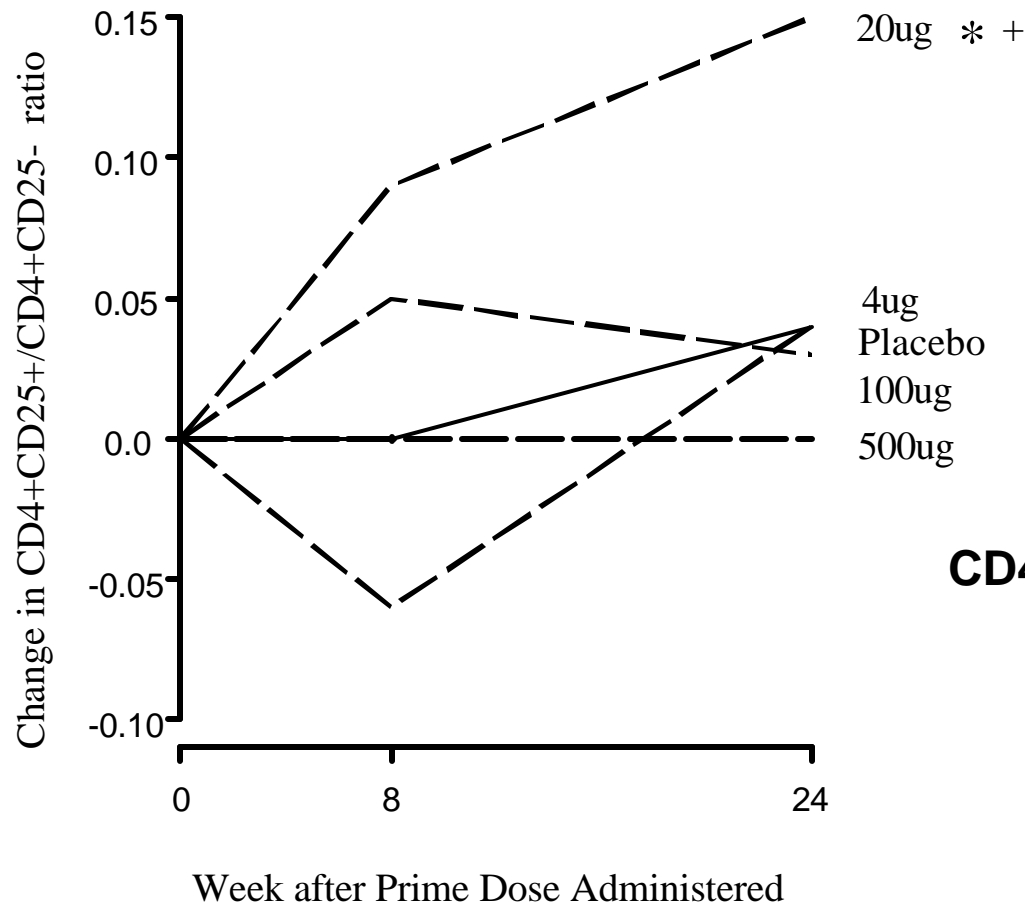


HbA1c rate of change per month compared to placebo group.

- HbA1c in the placebo group increased by 0.07 percent/month ($p < 0.005$).

Rate of change compared to placebo			
Microgram	Mean difference (percent/month)	95% CI	p-value
4	-0.05	(-0.12, 0.03)	0.20
20	-0.09	(-0.17, -0.02)	<0.01
100	-0.07	(-0.14, 0.00)	0.06
500		ongoing	

CD4+CD25+ T cells increased in the 20 mg dose group.



**At 20 mg
CD4+ CD25+ T cells correlate to:
fasting (p=0.001)
stimulated (p=0.04)
c-peptide.**

SUMMARY AND CONCLUSIONS

- **No study-related adverse events.**
- **Transient enhancement of GAD65Ab after 500 mg.**
- **Fasting c-peptide increased after 20mg.**
- **HbA1c was lower after 20 mg compared to placebo.**
- **The increase in CD4+CD25+ T cells correlated to c-peptide.**
- *Ongoing analyses to test T cell parameters:*
 - *ELISPOT - Paul Lehman*
 - *GAD65 Tetramers: Gerald Nepom*

- Low dose alum-formulated GAD65 did not enhance GAD65Ab.**
- **GAD65 may have immunomodulatory effects on residual beta cells:**
 - a) c-peptide increase correlated to decreased HbA1c;**
 - b) c-peptide increase correlated to increased numbers of Treg cells.**
- *Phase III clinical studies are needed to confirm safety and efficacy.*

ACKNOWLEDGEMENT

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