

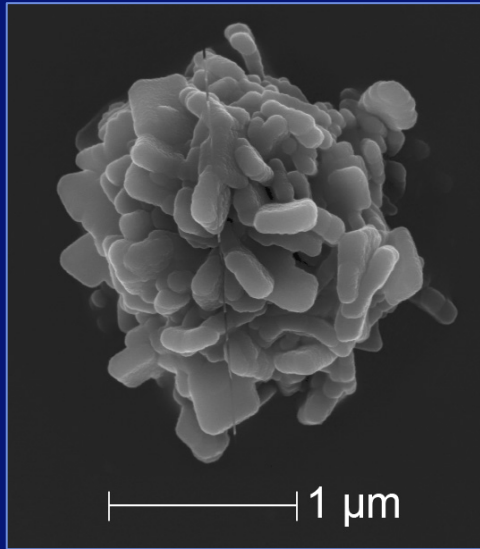
MannKind Corporation

Pulmonary Administration of GLP-1 Technosphere[®] Powder Elicits Dose- dependent Insulin Response

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GLP-1 Technosphere[®] Microparticles

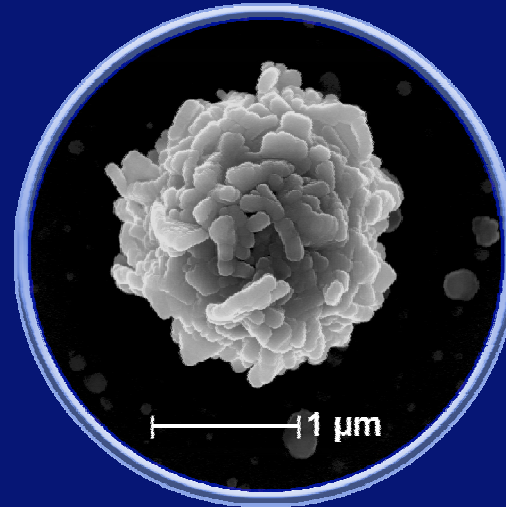
Technosphere[®]
microparticles



Water



GLP-1 Technosphere[®]



+

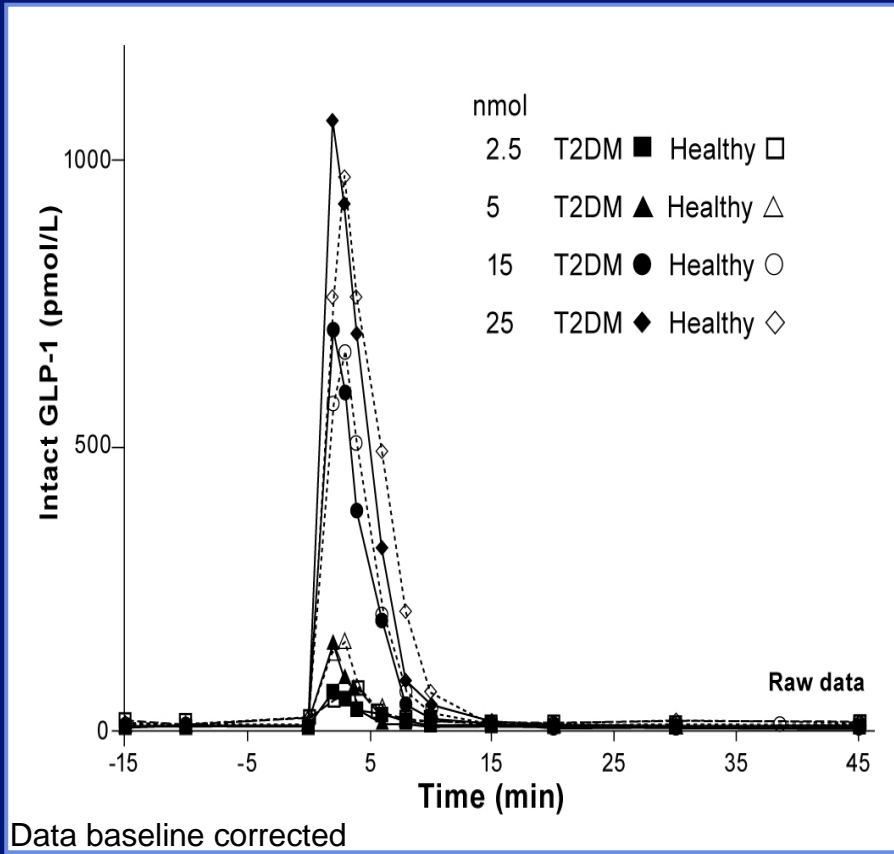


GLP-1



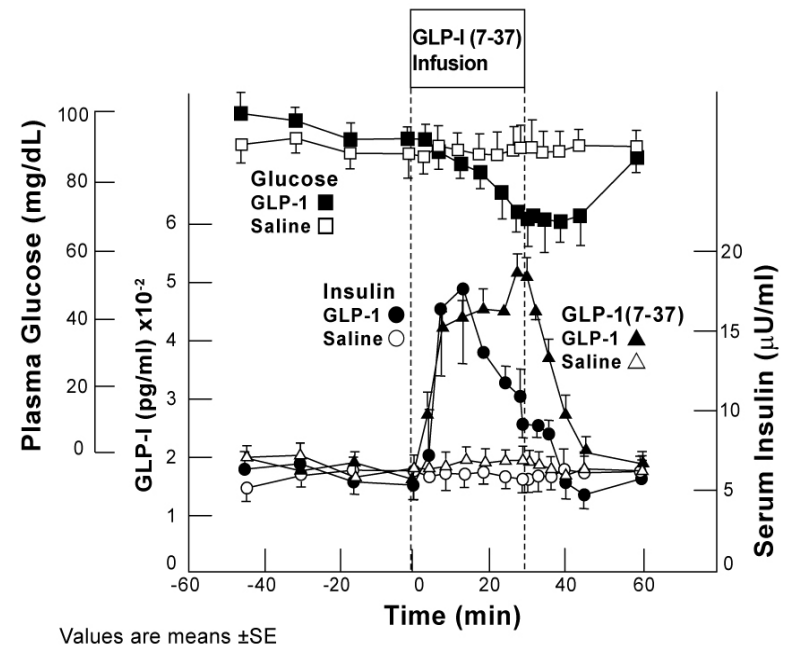
GLP-1 PK and PD

Vilsbøll 2003



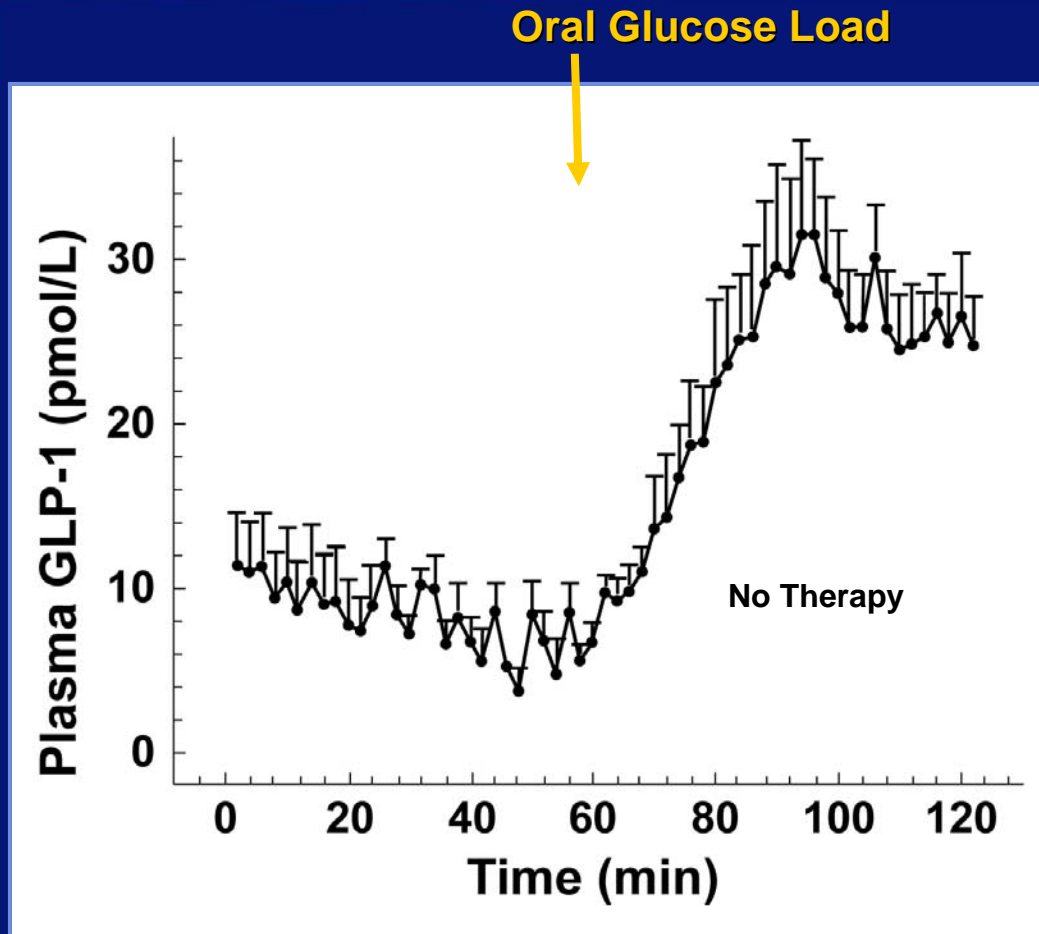
Nathan 1992

Insulinotropic actions of glucagonlike peptide GLP-1(7-37) infusion at a rate of $5 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 30 minutes in 3 nondiabetic fasting subjects



Vilsbøll T, et al. *J Clin Endocrinol Metab.* 2003;88(1):220-224.
 Nathan DM, et al. *Diabetes Care.* 1992;15(2):270-276.

Pattern of GLP-1 Release –Prandial Pulsatility–



- GLP-1 secreted in a pulsatile manner
- Rapid GLP-1 release following glucose ingestion

Balks HJ, et al. *Journal of Clinical Endocrinology and Metabolism*. 1997;82:786-790.

Prandial Dosing and Weight Loss

- After 5 days prandial (PSI) dosing 30 minutes before the meal vs. continuous sc infusion (CSI)
 - ✦ 15% reduction in mean food intake on Day 5 was significantly lower with GLP-1 when compared to placebo ($P=0.02$, pooled data)
 - ✦ Gastric emptying rate was reduced with both PSI ($P=0.001$, Days 1 and 5) and CSI ($P=0.02$, Day 1 only) when compared to placebo
 - ✦ 0.55 kg weight loss between beginning and ending treatment with PSI ($P<0.05$)

PSI – prandial subcutaneous injection
CSI – continuous subcutaneous infusion

Näslund, E., et al. Prandial sc injections of GLP-1 cause weight loss in obese human subjects. *British Journal of Nutrition*. 2004;91(3):439-446.

Acute Response to GLP-1

Pharmacology		Significant Adverse Event	
	insulin secretion		reduced well-being
	↓ fasting & PP glucose		nausea
	delayed gastric emptying		profuse sweating
	↓ food intake / ↑ satiety		vomiting
	↑ heart rate		headache
	↑ blood pressure		

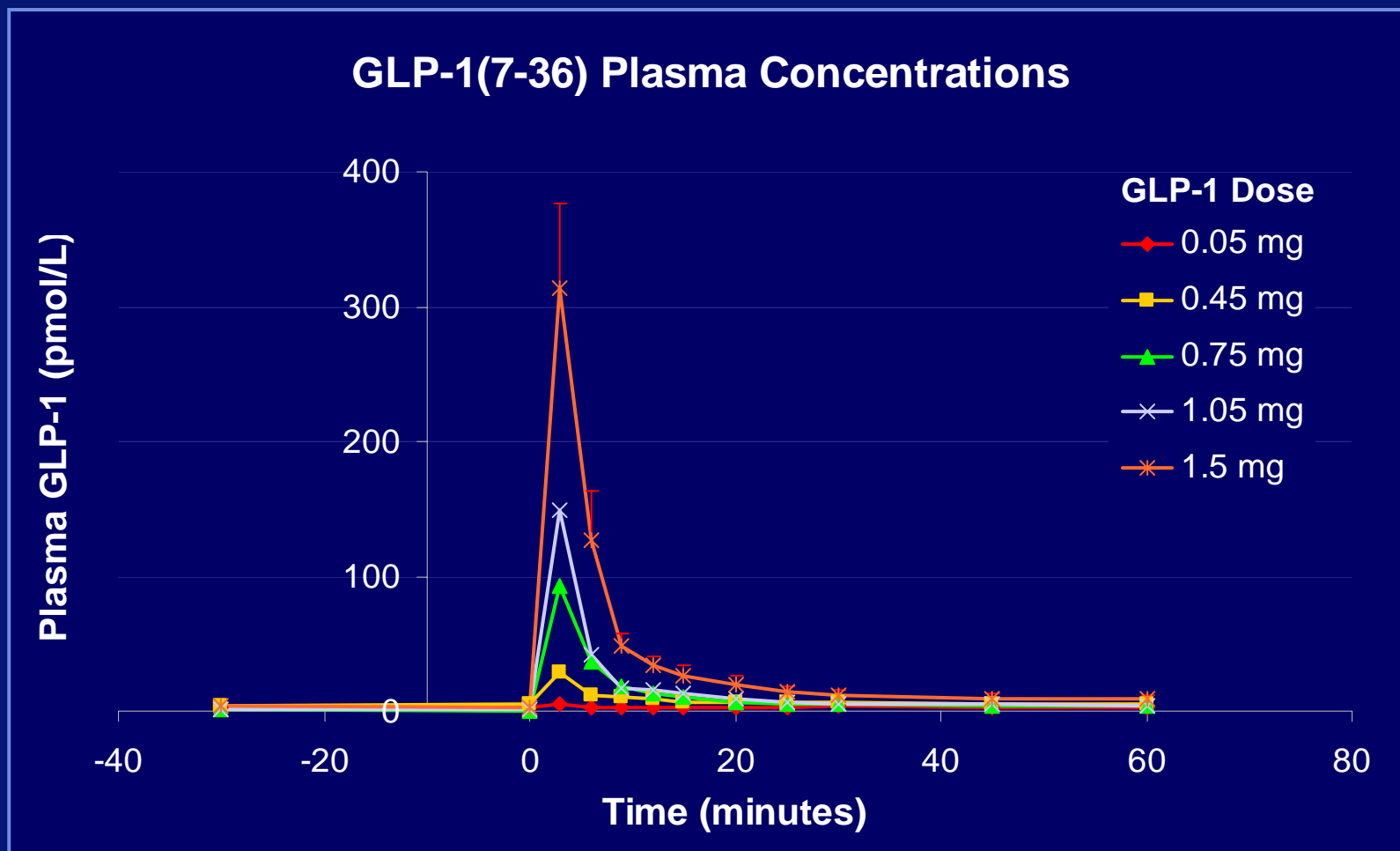
FHD Clinical Trial MKC-253-001

- Phase 1a, Single-Dose, Open-Label, Ascending Dose, Controlled Safety and Tolerability Trial of MKC253 Inhalation Powder in Healthy Adult Male Subjects
 - ✦ Single site
 - ✦ N=26, fasted
 - ✦ GLP-1 doses: 0.05 mg, 0.45 mg, 0.75 mg, 1.05 mg, 1.5 mg
 - ✦ Primary endpoint: tolerability (e.g., PE, vitals, labs, AEs)
- Secondary endpoints:
 - ✦ PK: plasma GLP-1 and FDKP
 - ✦ Safety: PFTs, ECGs, etc.

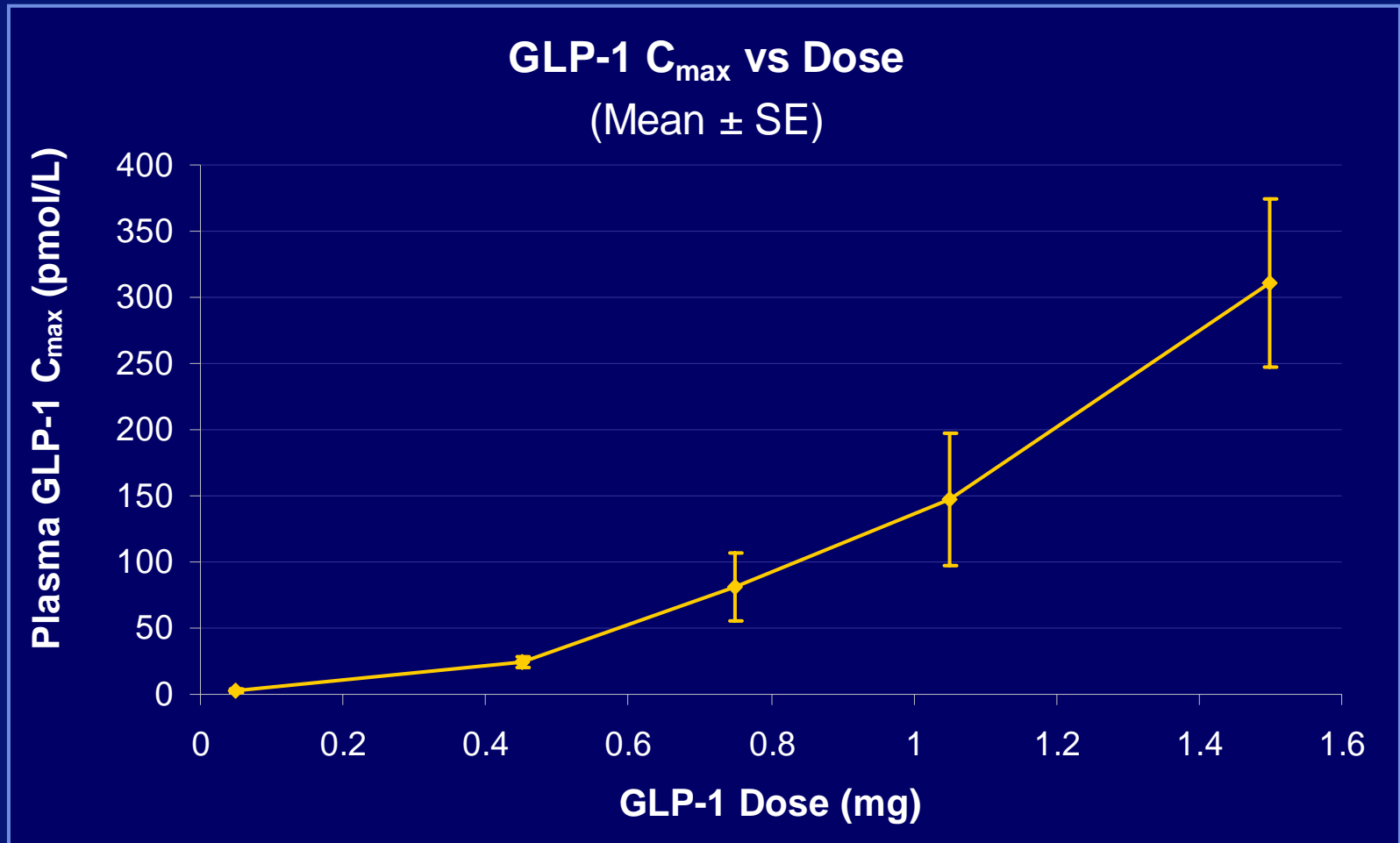
MKC-253-001 Demographics

Demography						
Dose Group	0.05 mg	0.45 mg	0.75 mg	1.05 mg	1.5 mg	Total
Enrolled	4	4	6	6	6	26
Age (yr)	22.5	22.8	25.2	24.0	21.7	23.3
Weight (kg) Mean	75.70	77.10	80.00	72.45	78.45	76.79
BMI Mean	22.50	22.53	22.67	21.88	22.55	22.41

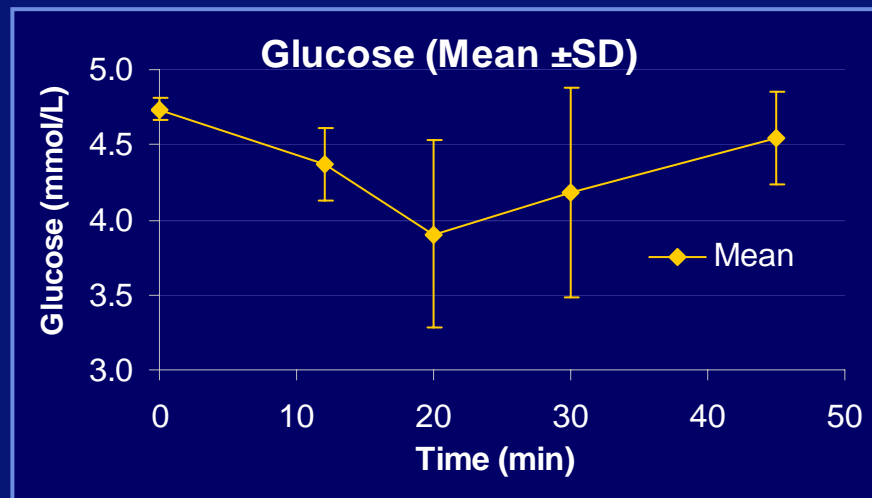
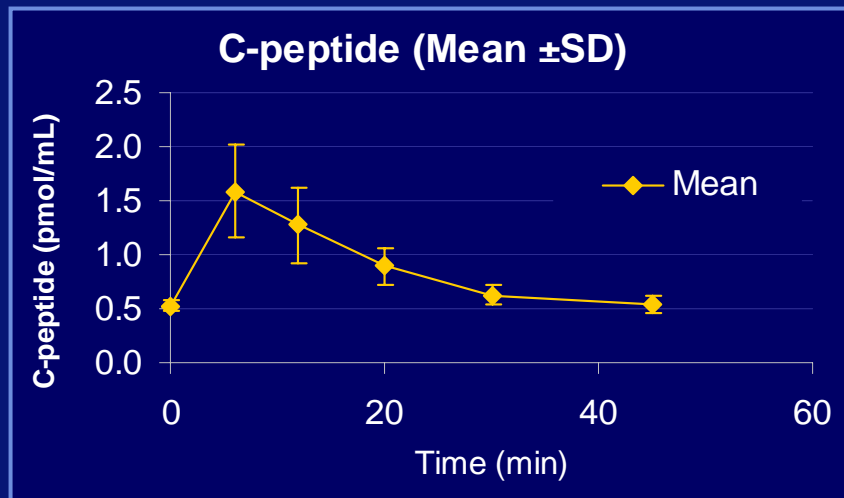
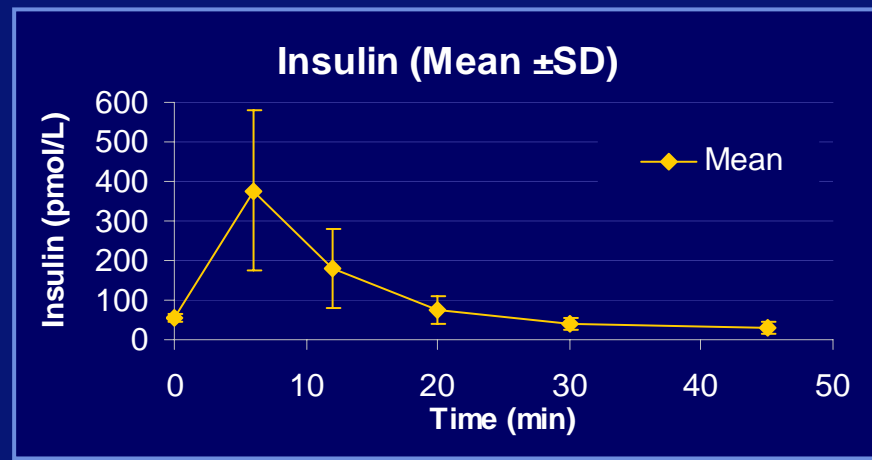
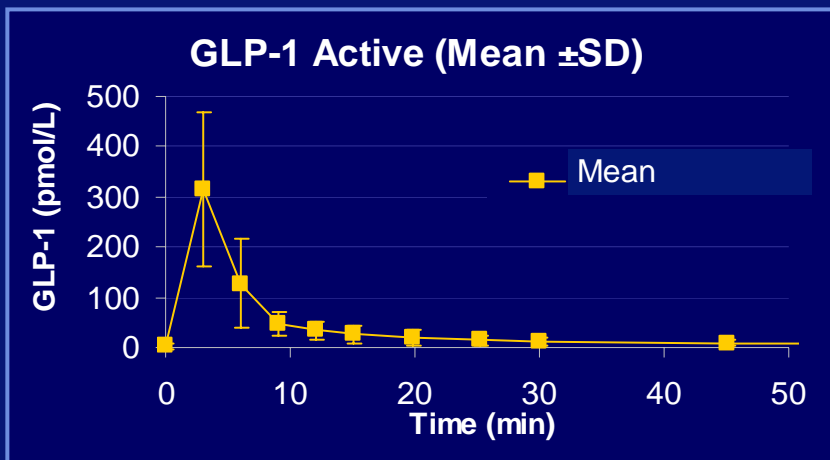
MKC-253-001: GLP-1 Dose Response



MKC-253-001: GLP-1 Concentration is Dose Dependent



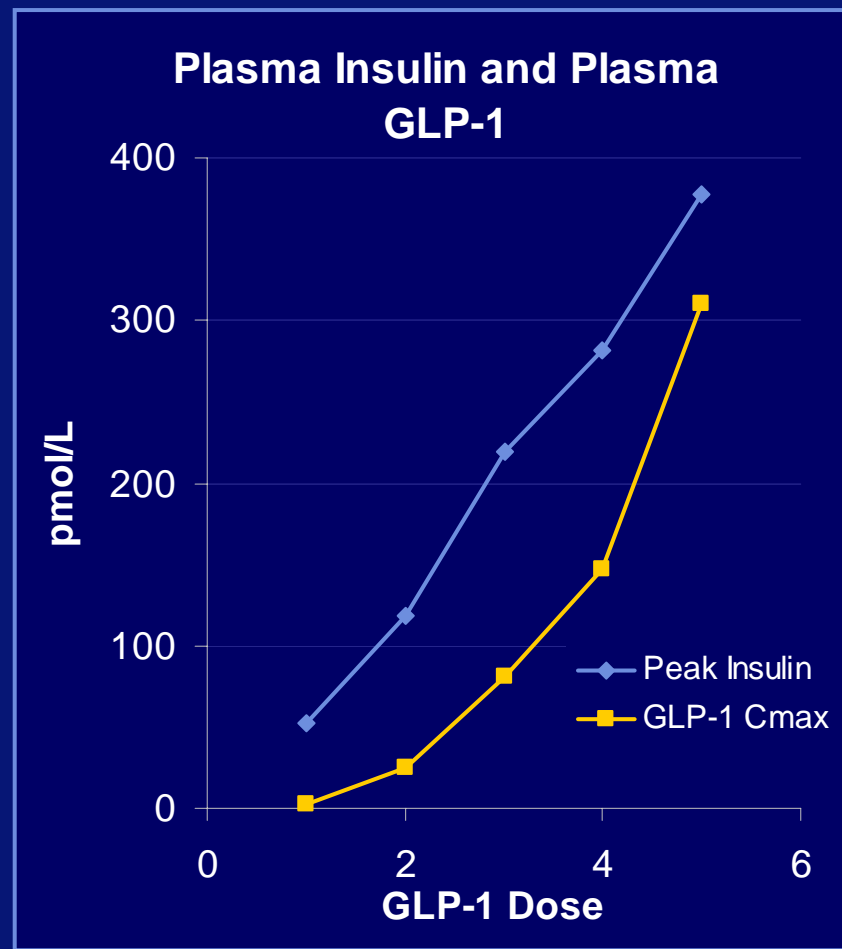
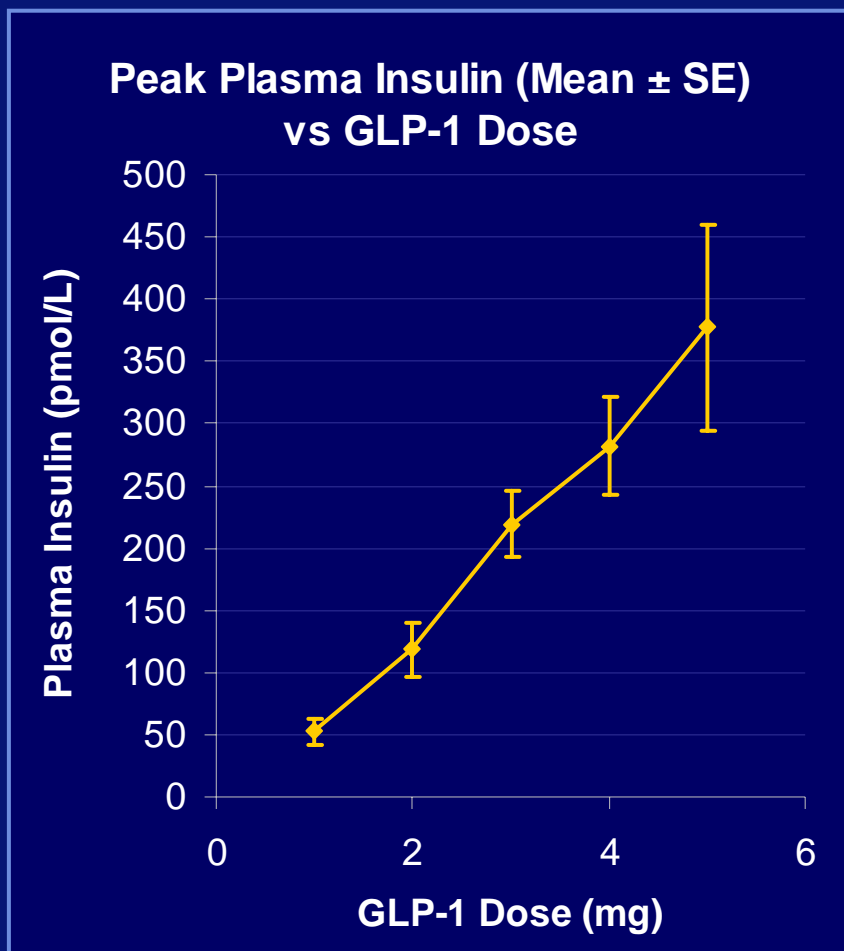
MKC-253-001 Cohort 5: 1.5 mg Summary



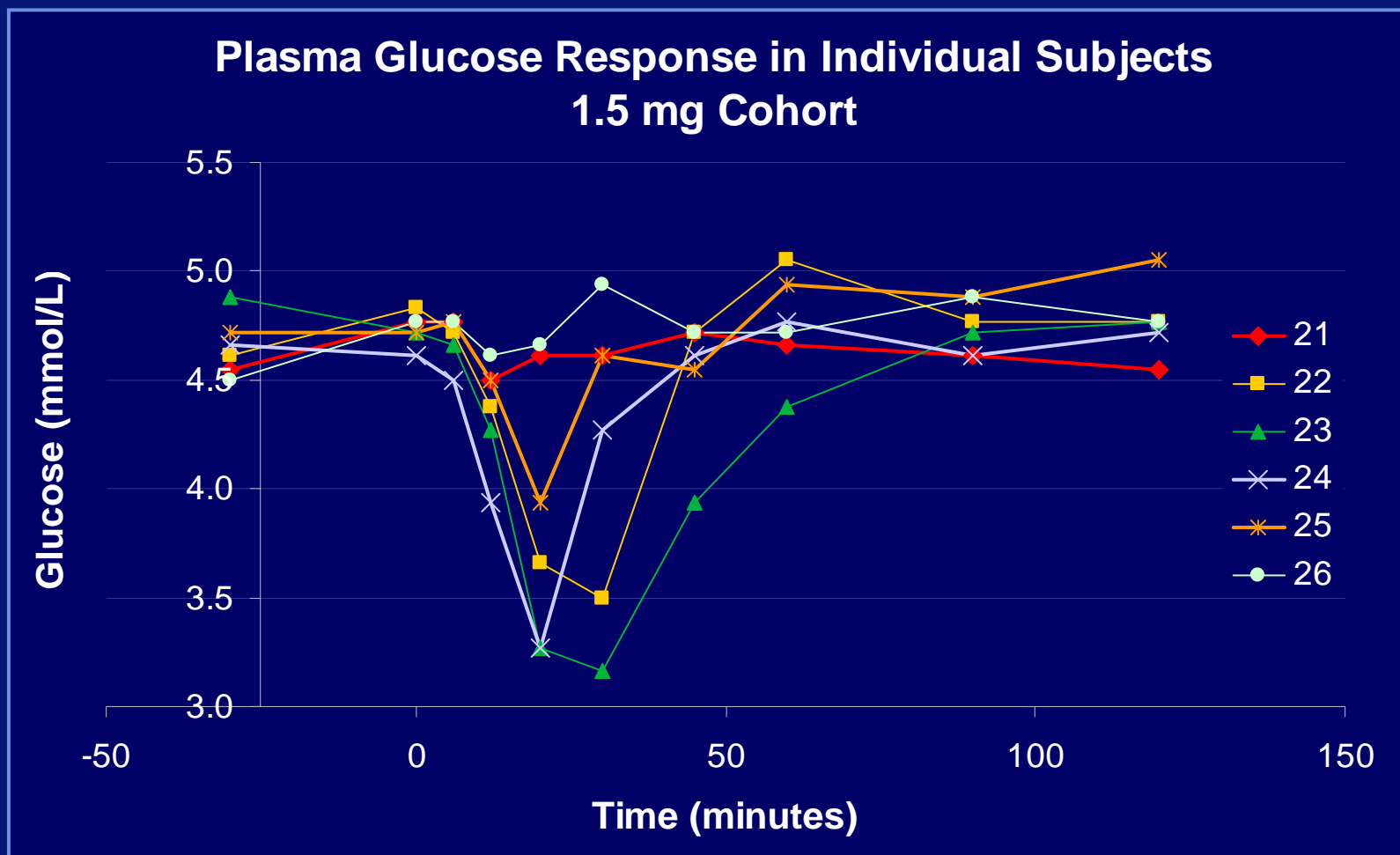
MKC-253-001: Dose Relationships

–Insulin Response is Dose Dependent–

–Insulin and GLP-1 C_{max} –



MKC-253-001: Individual Glucose Responses at 1.5 mg



MKC-253-001: Adverse Event Summary

Adverse Event	Number of Subjects with AEs					
	0.05 mg	0.45 mg	0.75 mg	1.05 mg	1.5 mg	Total
Cough	2		2	3	3	1
Dysphonia			1			1
Productive cough				1		1
Throat irritation				1		1
Headache	1	1		1	1	4
Dizziness					2	2
Dysgeusia*			1			1
Fatigue			1	1	1	3
Seasonal allergy				1		1
Rhinitis				1		1
Increased appetite					1	1

* Bad taste in mouth

AEs recorded from screening to follow-up

Comparative Adverse Events: IV vs Pulmonary GLP-1 Administration

Adverse Event	IV[†] (16.7 mcg)	IV^{†*} (50 mcg)	Pulmonary* (1.5 mg)
Reduced well-being	42%	100%	17%
Nausea	33%	83%	0%
Profuse sweating	17%	67%	0%

* Comparable C_{max}

[†]VilSBoll et al. *Diabetes Care*. June 2000.

Acute Response to GLP-1 Technosphere®

Pharmacology		Significant Adverse Event	
✓	insulin secretion	✗	reduced well-being
✓	↓ Fasting glucose	✗	nausea
?	↓ PP glucose	✗	profuse sweating
?	delayed gastric emptying	✗	vomiting
?	↓ food intake / ↑satiety	✓	headache
✓	↑ heart rate		
✓	↑ blood pressure		

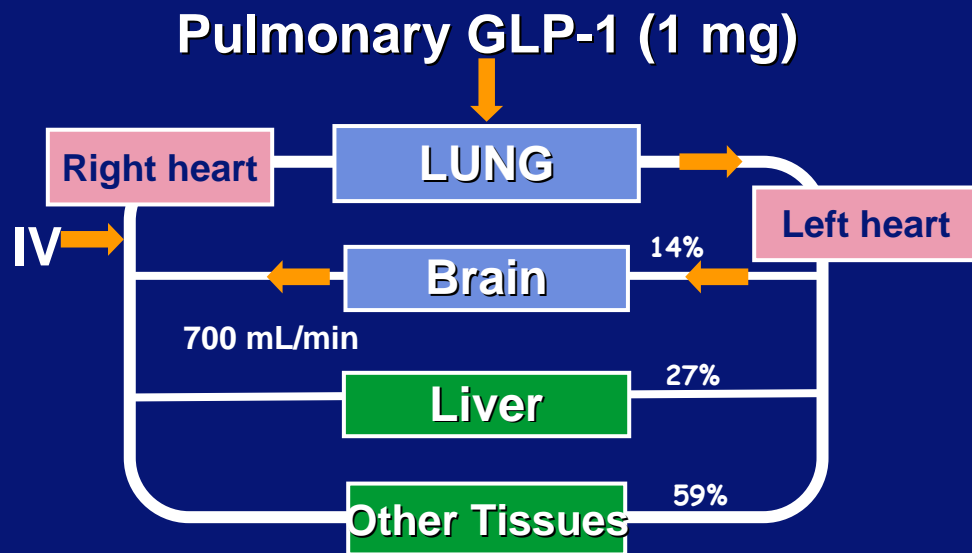
Summary

- **Pulmonary delivery of MKC253 results in:**
 - ✦ High circulating concentrations of GLP-1
 - ✦ Dose dependent insulin release
 - ✦ Reduction in fasting plasma glucose
 - ✦ No nausea or vomiting
- **Next steps:**
 - ✦ MKC-253-002 in fasted and fed subjects with T2DM – ongoing
 - ✦ Data suggest that Pulmonary GLP-1 more closely mimics normal, prandial GLP-1 release

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Distribution of Intact GLP-1 to Brain and Liver: Pulmonary vs. IV Administration Model



After 1 minute 1mg of GLP-1 administered via pulmonary route results in 2X the intact GLP-1 (μg) compared with IV administration