



Two and Four Hour Tests Differ in Capture of C-peptide Responses to a Mixed Meal

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Presenter Disclosure Information

No relationships to Disclose

Outline

- Background
- Methods
- 2 & 4 hr correlation
- Variability of estimates
- Timing of peak C-peptide
- Deviation from gold standard
- Conclusions

Background

- MMTT commonly used after diagnosis of T1D.
- Test performed differently: 4 hr vs. 2 hr abbreviated test.

2 Hr Advantages	4 Hr Advantages
Reduces subject burden	Pattern of response varies across individuals
Pediatrics may develop hypoglycemia towards end of 4 hr test	2 hr test misses full hormonal response
Peak C-peptide usually occurs during 1 st 2 hours	T1D patients may have delayed insulin secretory response; 2 hr test may not capture all of response

- Evaluate C-peptide response for 2 and 4 hr MMTT.

Methods

- Data from 3 Immune Tolerance Network (ITN) clinical trials: START (ATG), T1DAL (Alefcept), AbATE (Anti-CD3).
- 186 control & drug treated subjects with new-onset T1D.
- Mean(SD) age of 16.8 (6.81).

START & T1DAL: 20; AbATE: 13

- 125 pediatrics, 61 adults
- Varying baseline peak C-peptide (pmol/mL) entry criteria
START: >0.4 , T1DAL: >0.2 , AbATE: NA (all > 0.3)
- C-peptide samples collected at 0, 15, and 30 minutes and every 30 minutes thereafter up to 4 hrs.
- MMTT at baseline, month 12 and month 24.
- C-peptide AUC computed using the trapezoidal rule.

2 and 4 Hr AUC Correlation

Visit	Correlation Coefficient
Baseline	0.959
Month 12	0.977
Month 24	0.986

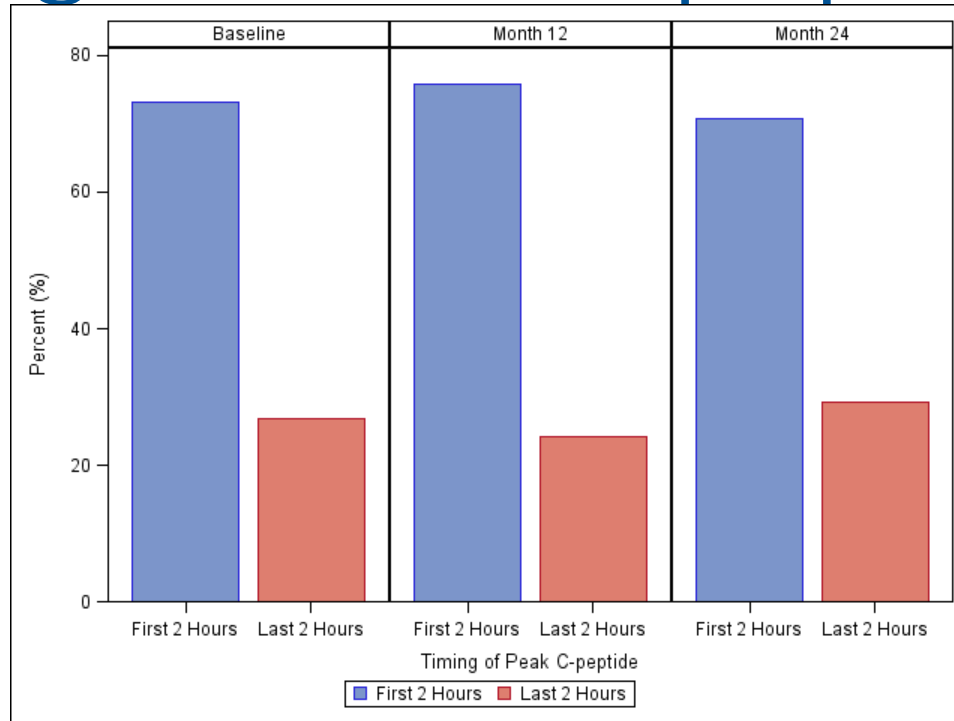
- Correlation high across all visits, treatment and age groups.

2 and 4 Hr C-peptide mAUC Estimates

Visit	2 Hr mAUC		4 Hr mAUC	
	Mean	SD	Mean	SD
Overall	0.64	0.46	0.64	0.41
Baseline	0.78	0.37	0.78	0.32
Month 12	0.64	0.46	0.63	0.42
Month 24	0.48	0.49	0.49	0.46

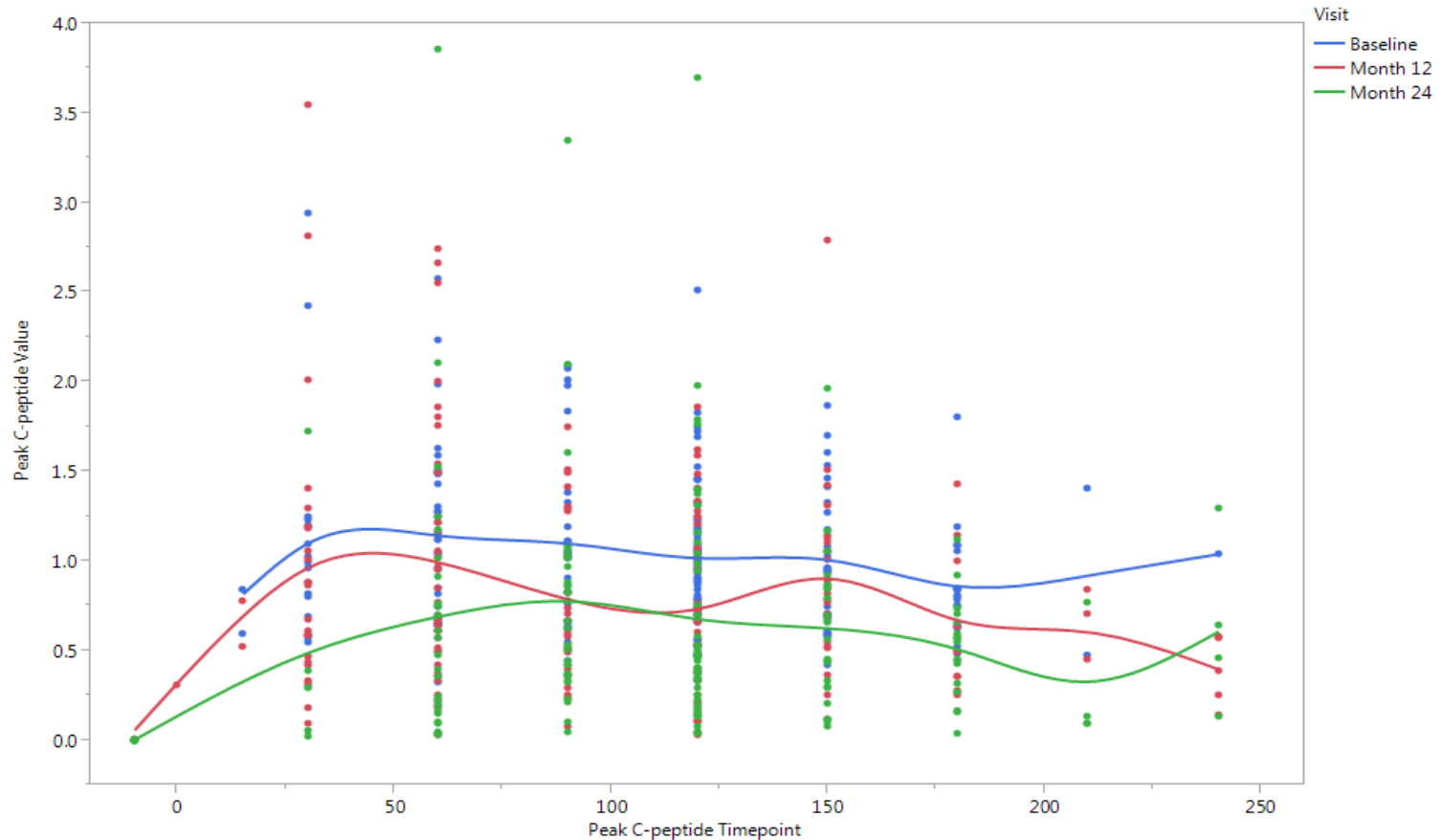
- 2 and 4 hr mean AUCs comparable across visits.
- 2 hr SD > 4 hr SD.
- Trend consistent across age & treatment groups.
- Mean & SD similar for 2 & 4 hr change from baseline mAUC.

Timing of Peak C-peptide



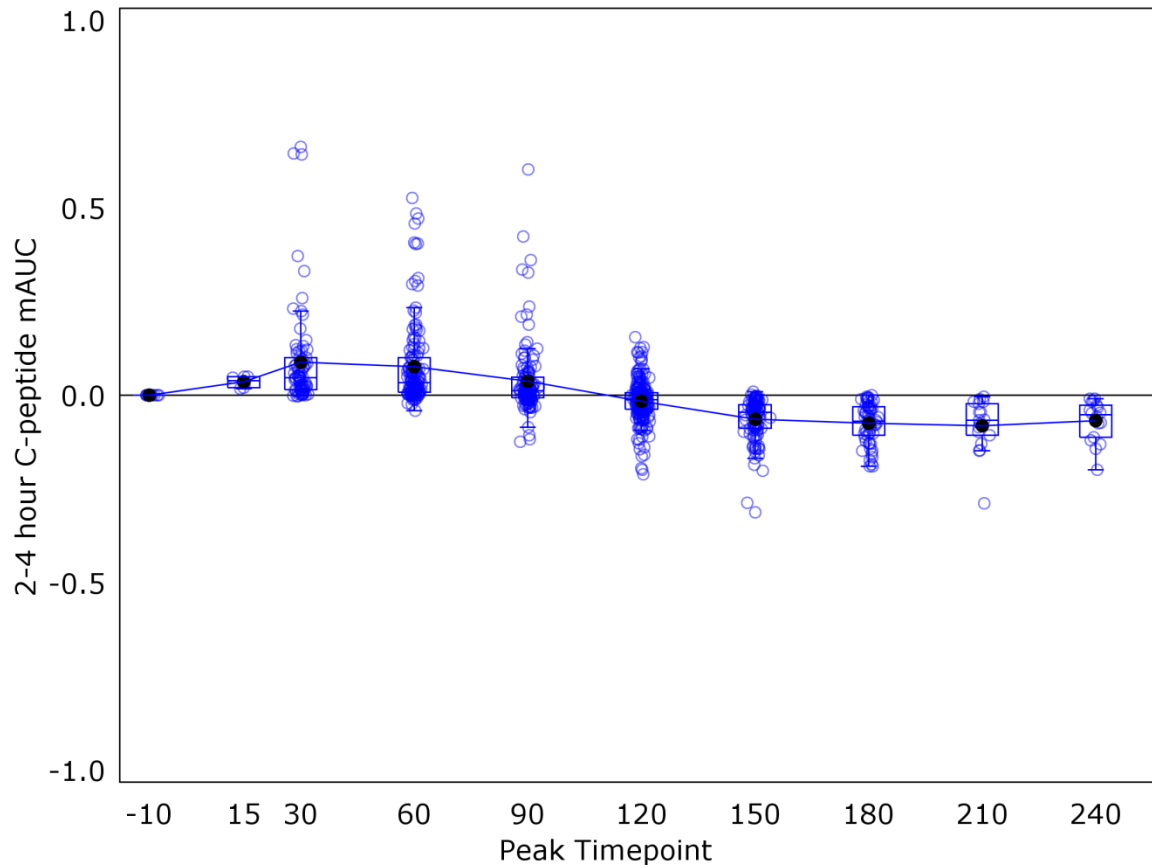
- Peak occurs in second 2 hrs of MMTT for ~25% of observations.
- Trend consistent across visits.
- Similar trend across studies at BL & M12.
- Month 24, peak occurring in 2nd 2 hrs:
 - START: 18%
 - T1DAL: 41%
 - AbATE: 31%

Peak C-peptide Value by Peak Time Point



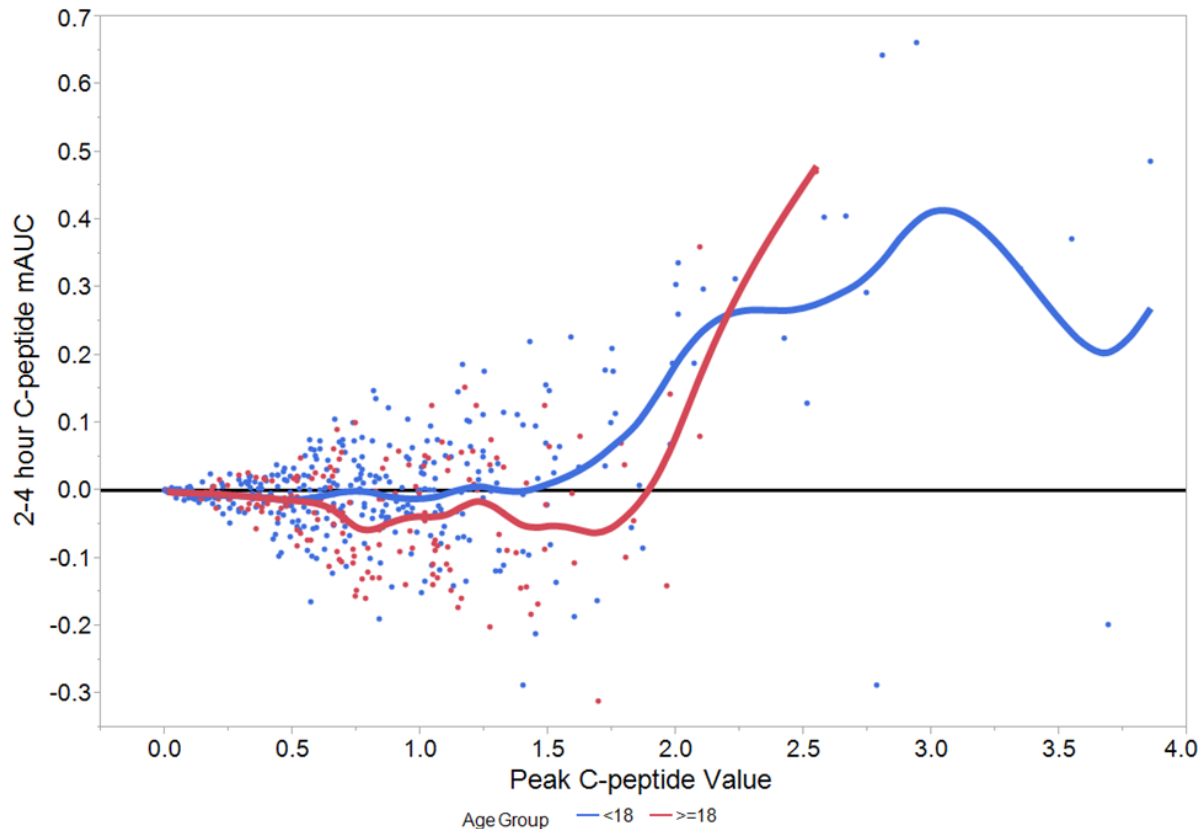
- Value of peak C-peptide still reasonably high when peak occurs in 2nd 2 hrs compared to 1st 2 hrs.

2-4 Hr C-peptide mAUC by Time of Peak



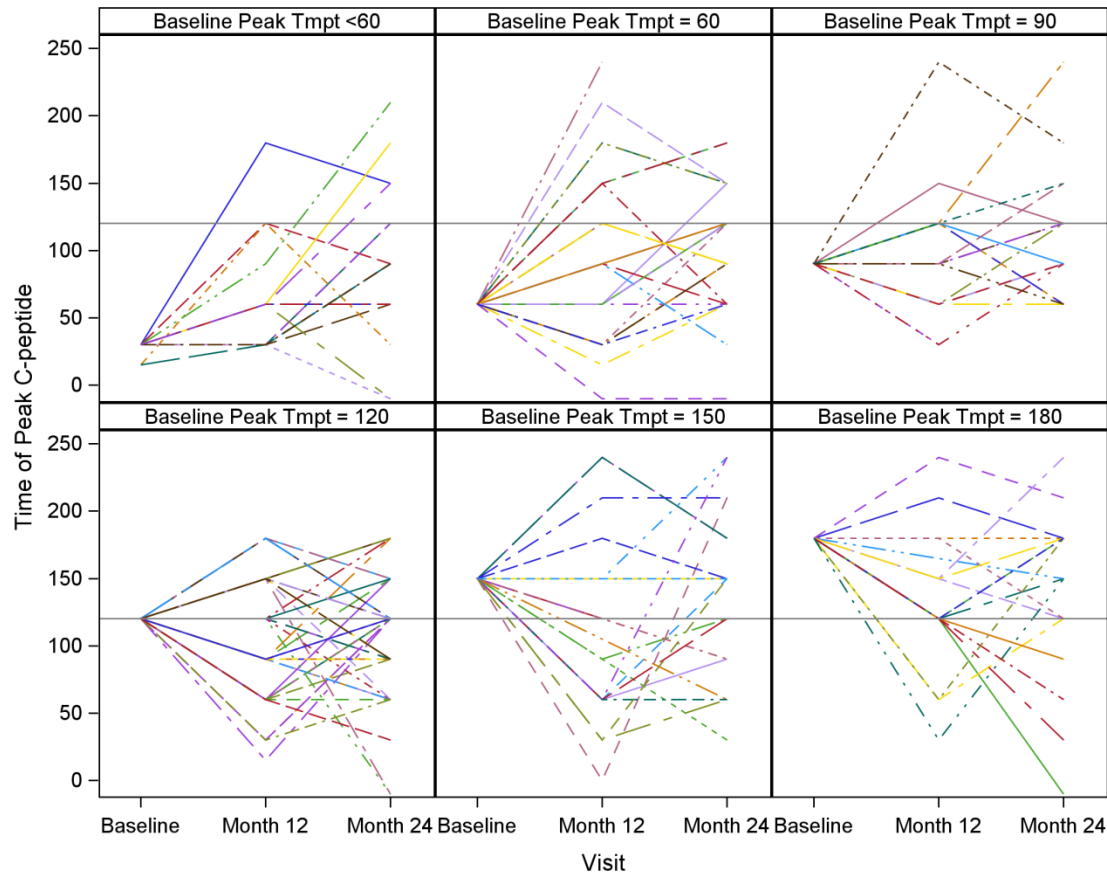
- Earlier peak \longrightarrow greater proportion of total 4 hr AUC captured at 2 hrs.

2-4 Hr C-peptide mAUC by Peak Value & Age



- Large peak C-peptide, 2 hr mAUC > 4 hr mAUC.
- Adult subjects tend to have more area in 2nd two hrs of MMTT compared to pediatrics.

Time of Peak Changes Within Subject Over Time



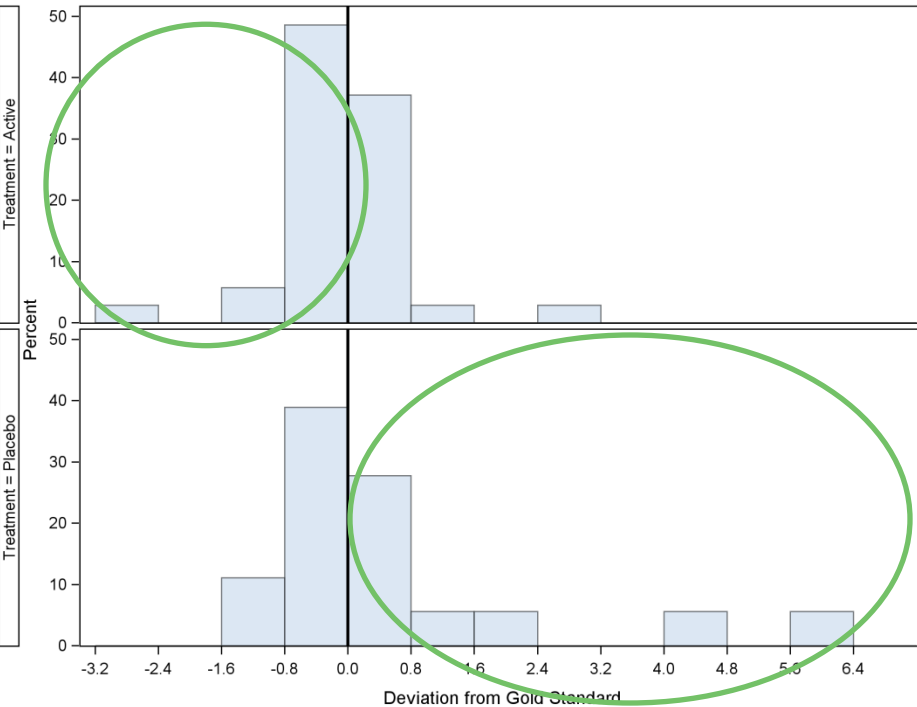
- The time of the peak C-peptide varies within subject over time.
- Smaller proportion of data is captured with 2 hr test if peak becomes later for an individual.

Deviation from Gold Standard

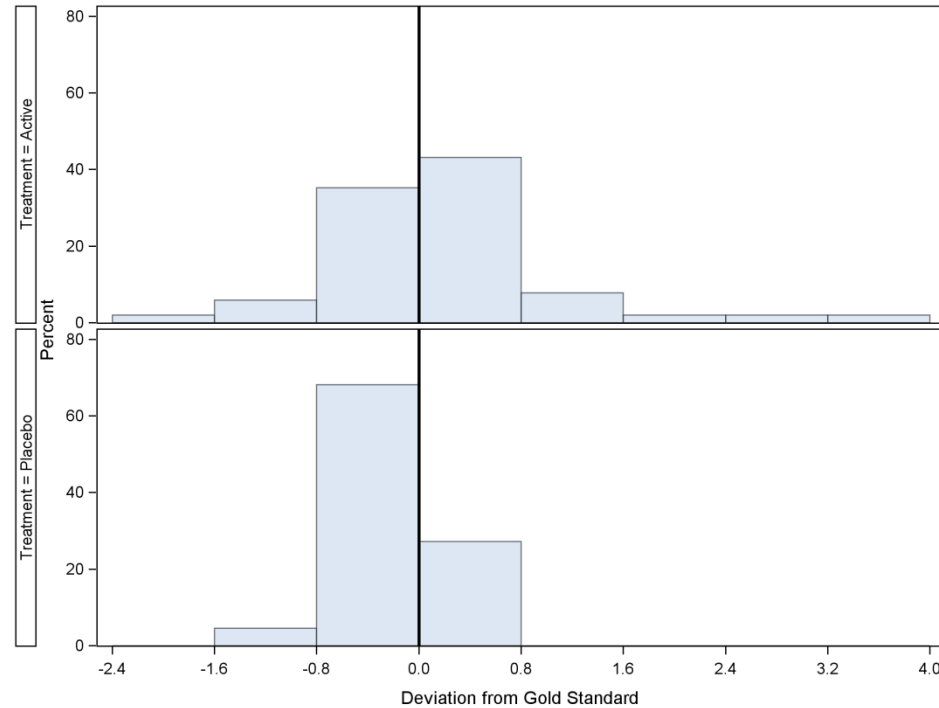
- Assume 4 hr mAUC represents gold standard
- Deviation from gold standard= $(2 \text{ hr mAUC} - 4 \text{ hr mAUC}) / \text{SD}$
- Positive values \Rightarrow more area amassed during 1st 2 hrs
 - 2 hr mAUC too high
- Negative values \Rightarrow less area amassed during 1st 2 hrs
 - 2 hr mAUC too low
- Imbalances in deviation profiles between treatment groups could be cause for concern.

Distribution of Deviation from Gold Standard

Deviation from Gold Standard at Month 12 for START



Deviation from Gold Standard at Month 12 for AbATE



- Largest imbalance seen in START.
 - Distribution of deviation among placebo subjects shifted to the right (positive, 2 hr mAUC too high)
 - Shifted to left for treated subjects (negative, 2 hr mAUC too low).
- Direction of deviation opposite for AbATE.

Conclusions

- 2 and 4 hr MMTT strongly correlated.
- Standard deviation larger for 2 hr test.
- Shorter test may under- or overestimate levels.
- Differences between the 2 measurements should be considered when developing study endpoints.

Collaboration

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Questions?