

# PP04 Cross-Study Vehicle Effect Analysis Using SEND Data

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## Introduction

CDISC SEND team proposed a clear and unambiguous structured description of the study vehicle in the draft major SENDIG v4.0 release. To pilot the usefulness of this, a cross-study vehicle effect analyses project using current SEND data was performed by extracting vehicle and dose volume information from study protocols and reports. The vehicle component names were standardized to match the Preferred Substance Name from FDA's Global Substance Registration System. We explored the relationship between preclinical study numeric endpoints such as clinical pathology, body weight and organ weight with a subset of widely used vehicle components; detected statistically significant differences attributed to vehicle components; explored potential dose-relationships between the numeric endpoints and the concentration of the vehicle components; and gained knowledge to inform decisions regarding initiatives to reduce the number of concurrent control animals required on toxicology studies.

## Methodology & Preliminary Results

### 1. Studies and Endpoints

| Site | Species | #Studies | Length |
|------|---------|----------|--------|
| BMS  | Monkey  | 46       | 1M     |
| BMS  | Dog     | 36       | 1M     |
| BMS  | Rat     | 27       | 1M     |
| CRO  | Rat     | 24       | 1 - 6M |
| CRO  | Monkey  | 30       | 1 - 6M |

- Body Weight Percent gain
- Numeric lab results value/fold change
- Organ Weight

### 4. Studies With vs Without

| Study   | Components     | SET of C1    |
|---------|----------------|--------------|
| Study 1 | C1, C3, C5     | WITH (C1)    |
| Study 2 | C1, C4         | WITH (C1)    |
| Study 3 | C2, C3         | To Exclude   |
| Study 4 | C2, C5         | To Exclude   |
| Study 5 | C2, C6, C8, C9 | Without (C1) |

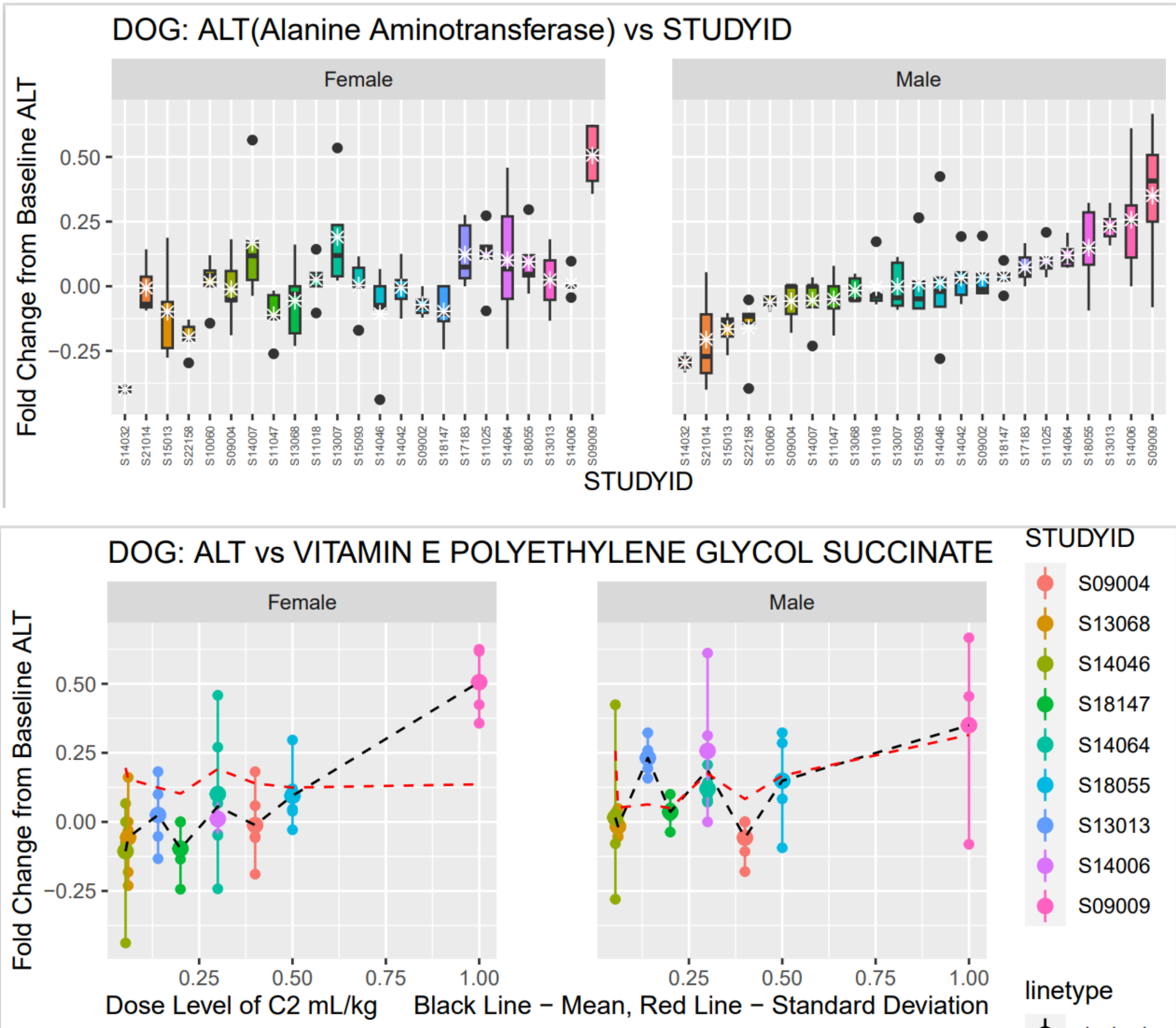
### 2. Vehicle Standardization & Summary

5% ethanol ,15% d-alpha tocopheryl  
polyethylene glycol 1000 succinate,  
80 % polyethylene glycol 400 (w/w/w/w)

| Component Name                          | Value | Units |
|-----------------------------------------|-------|-------|
| ALCOHOL                                 | 5     | %     |
| VITAMIN E POLYETHYLENE GLYCOL SUCCINATE | 15    | %     |
| POLYETHYLENE GLYCOL 400                 | 80    | %     |

| Code | SPECIES | Component Name                          | #Stu | #Val |
|------|---------|-----------------------------------------|------|------|
| C1   | MONKEY  | POLYSORBATE 80                          | 10   | 4    |
| C2   | MONKEY  | VITAMIN E POLYETHYLENE GLYCOL SUCCINATE | 12   | 5    |
| C3   | MONKEY  | POLYETHYLENE GLYCOL 400                 | 10   | 7    |
| ...  |         |                                         |      |      |
| C1   | DOG     | POLYSORBATE 80                          | 7    | 5    |
| C2   | DOG     | VITAMIN E POLYETHYLENE GLYCOL SUCCINATE | 13   | 6    |
| C3   | DOG     | POLYETHYLENE GLYCOL 400                 | 14   | 9    |

### 3. Relationship

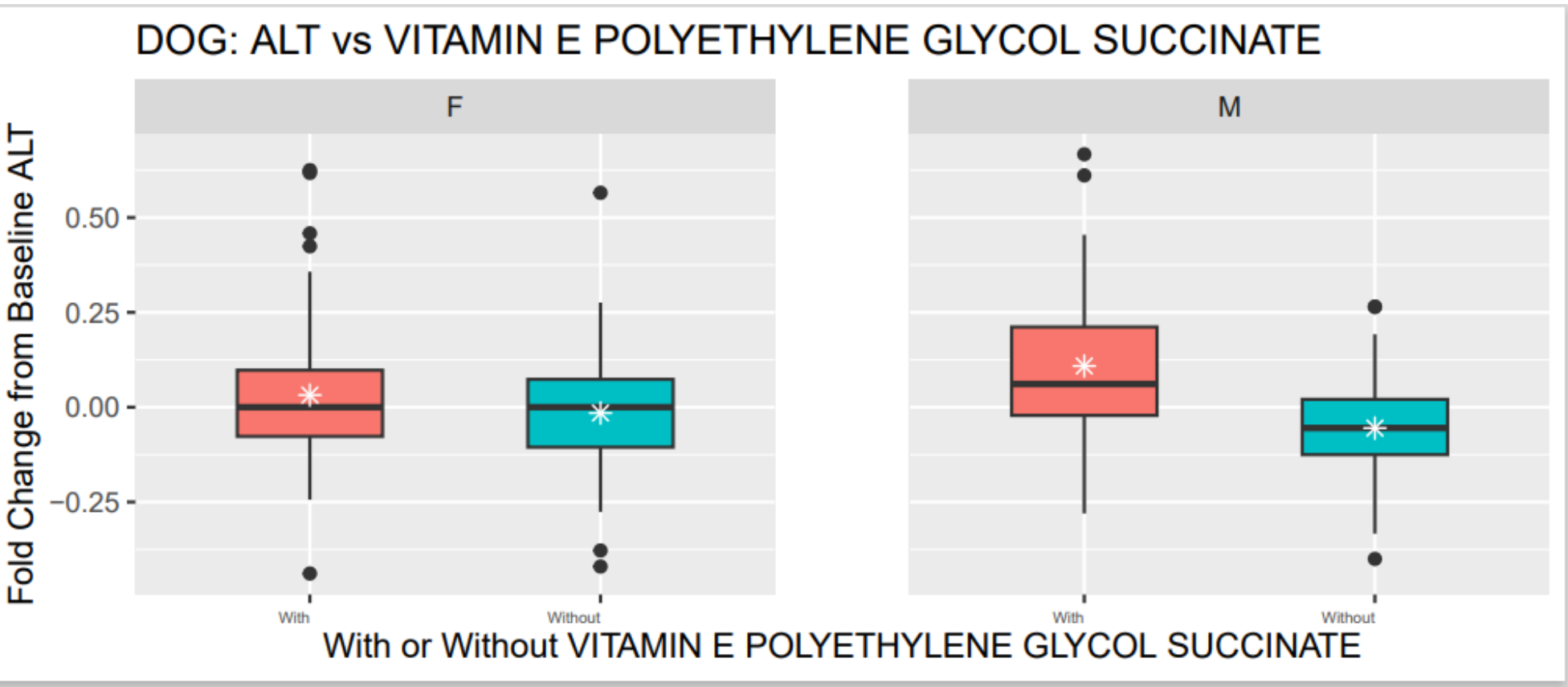


### 5. Statistical analysis and report

- Run Welch Two Sample t-test between studies with and without a component and its associated components. Adjust p values for multiple comparison by the Benjamini & Hochberg ("BH") method.
- Report statistically significant differences: at adjusted p value of <0.001 and <0.005

LB Fold Change over Baseline Component: C1, C2

| SPECIES | SEX | CAT  | TEST | Com-<br>ponent | Mean<br>diff | BH Adj.<br>P-value |
|---------|-----|------|------|----------------|--------------|--------------------|
| MONKEY  | F   | CHEM | GLOB | C1             | 0.10         | <0.001             |
| MONKEY  | M   | HEME | RET  | C1             | 0.55         | <0.001             |
| MONKEY  | M   | HEME | MPV  | C2             | -0.07        | <0.001             |
| DOG     | M   | CHEM | ALT  | C2             | 0.16         | <0.001             |
| ...     |     |      |      |                |              |                    |



## Summary & Reference

- The statistically significant differences identified suggest that certain vehicle components impact preclinical numeric endpoint values. However, we failed to identify a dose relationship between any of the numeric endpoints and the components evaluated.
- A clear and unambiguous structured description of the treatment vehicle makes this vehicle analysis possible. Further standardization to a tabulated vehicle component domain in SEND will dramatically reduce manual effort, human error, and facilitate broad access to curated data to mine for information on individual vehicle components.
- Increased accessibility to information regarding the potential effects of various vehicle components (e.g., PEG-400 and renal toxicity) can promote the judicious selection of vehicle formulation components and inform decisions related to vehicle control groups.

### Reference:

A comprehensive review of many vehicle effects is published in International Journal of Toxicology 2016, Vol. 35(2) Gad et al.  
<https://journals.sagepub.com/doi/pdf/10.1177/1091581815622442>

sendigR: Enable Cross-Study Analysis of CDISC SEND Datasets  
<https://phuse-org.github.io/sendigR/>  
FDA's Global Substance Registration System  
<https://precision.fda.gov/unisearch>