Algorithme Pharma

AN ALTASCIENCES COMPANY

Unique Full Service Provider Focused on Early Stage Clinical Research

Statistical Challenges – Human Abuse Liability Trials

Bijan Chakraborty

Principal Biostatistician

Advancement in Abuse Potential Assessments – Building on the FDA Draft Guidance for Industry, 16-17 April 2015

Bethesda North Marriott Hotel & Conference Center

FDA/NIDA/CCALC

Outline

- Overview of Human Abuse Liability (HAL) Trials
- Pharmacodynamics (PD) in HAL Trials
- Overall Statistical Responsibilities
- Sample Size Calculation
- Statistical Analysis
- Outliers in PD Endpoints
- PK-PD Relationship
- A Statistical Puzzle
- Concluding Remarks

Abuse Liability Studies

Human Abuse Liability Trial Overview

▪ Design	▪ Double Blind, Multi Period Crossover with washout between periods
▪ Treatments	▪ Placebo, 2-3 doses of Test and 2-3 doses of control
▪ Phases	▪ Screening, Dose Selection, Qualification, Treatment and Follow-up
▪ Evaluation	▪ Safety, Pharmacokinetic and Pharmacodynamic
▪ Drugs	▪ CNS Drugs, Drugs that are similar to other drug with known AL, Drugs that produce psychoactive effects e.g. sedation, euphoria
▪ Subjects	▪ Healthy Volunteers with history of Recreational Drug Use, Age 18 – 55 Years ▪ Approximately 30-40 subjects are randomized in treatment phase
▪ Duration	▪ Average: Screening (4 weeks), Qualification (1-2 weeks), Treatment (8-10 weeks), 1 week Follow-up - Total 3-4 months

Human Abuse Liability Trials

Pharmacodynamic (PD) Assessments

▪ Scales	▪ Subjective/physiologic measures; positive/negative/other; unipolar/bipolar; ordinal / continuous;
▪ Assessments	▪ Visual Analog Scale (>20), Bowdle VAS (13), Bond-Lader VAS (16), Drug Similarity VAS, ARCI (5), Subjective Drug Value, Choice Reaction Time (3), Divided Attention (6), Digit Symbol Substitution (2), Digital Vigilance (4), Pupillometry (1) On Average 20-30 scales for a HAL Trial
▪ Time points	▪ Pre-dose, 0.5, 1,2,3,4,6,8,10,12,24, sometimes up to 48,72 hours in each period
▪ Endpoints	▪ Peak (Emax), Trough (Emin), Time (TEmax or TEmin), AUE, AUE(0-2h), Max Change from Baseline (CFBmax)

Overall Statistical Responsibilities

1	Need Sufficient Knowledge of PK and PD Evaluation
2	Quality SAP for Safety/PK/PD for Qualification/Treatment Phases
3	Derive accurate Endpoints for all Safety, PK and PD Measures
4	Produce large number of Tables for PK and PD (often > 250)
5	Produce large number of PK, PD Figures (often > 100)
6	Line Charts, Bar Charts, Box-Plot, Dose-Response, Regression, PK-PD

To accomplish all these for a complex and large HAL trial is a Challenge

Sample Size Calculation

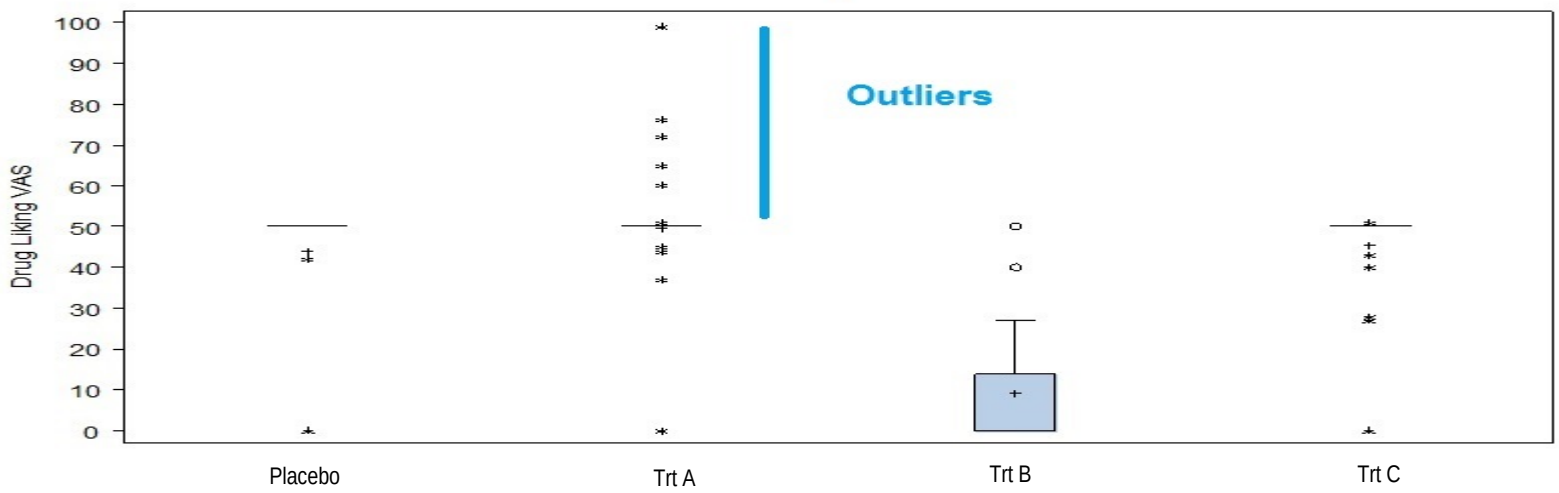
Mixed Model Analysis (ANCOVA)	Non-Parametric
▪ No Software Tool for Multi-Period Crossover adjusting for Period, Sequence and Carryover Effects	▪ Analysis do not adjust for Period, Sequence and Carryover Effects. ▪ Low Power means Larger Sample Size
▪ Using SAS Proc Power to Perform Model-based Power Analysis for Clinical Pharmacology Studies, Peng Sun, Merck & Co., Inc., PharmaSUG2010 - Paper SP05. http://www.pharmasug.org/cd/papers/SP/SP05.pdf Adjustment for only # of Periods.	▪ N/A
▪ > 1 primary endpoints: Low correlations between endpoints implies higher inflation in Sample Size. For 2 endpoints and 0.5 correlations, inflation is 25%. With 0.8 correlation, inflation is 17% ▪ Issue: Recruitment, Cost, Length of Study ▪ Source: Christy Chuang-Stein, "Challenge of multiple co-primary endpoints: A new approach", the 2007 ICSA Applied Statistics Symposium.	▪ Sample size will be much higher than ANCOVA analysis

Statistical Analysis

▪ 70 to 80% endpoints fail Normality/HOV test ▪ Non-parametric inferential analysis	▪ Possible risk of false negative results ▪ Do Generalized Linear Mixed Model (GLIMMIX) Analysis for Primary Endpoints?
▪ When Period, Sequence or Carryover is significant	▪ Investigate and explain the reasons ▪ Additional analysis if necessary
▪ 4X4 or 6x6 HAL Trial in Williams Square	▪ Not sufficient DF for Treatment by Carryover interaction if required
▪ Large variability on Subjective Measures	▪ Is it due to scale property or reliability of data from few subjects? ▪ Risk of False Negative Results
▪ Missing value imputation	▪ No issue, if Endpoints are estimable ▪ Not performed due to large # of Endpoints ▪ What is appropriate method for HAL data?

Outliers in PD Endpoints

Figure 14.2.3.1.3.1: Boxplots of Drug Liking VAS Emin
Per Protocol Population



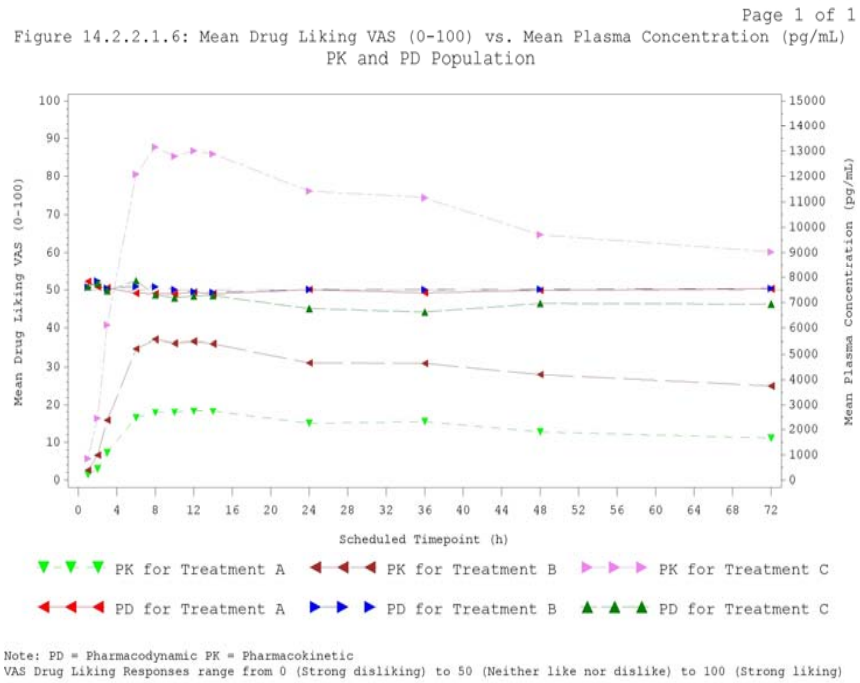
Note: Responses range from 0 (Strong disliking) to 50 (Neither like nor dislike) to 100 (Strong liking)
Data Source: Table 14.2.3.1.2.1

Not uncommon to see many outliers for some endpoints

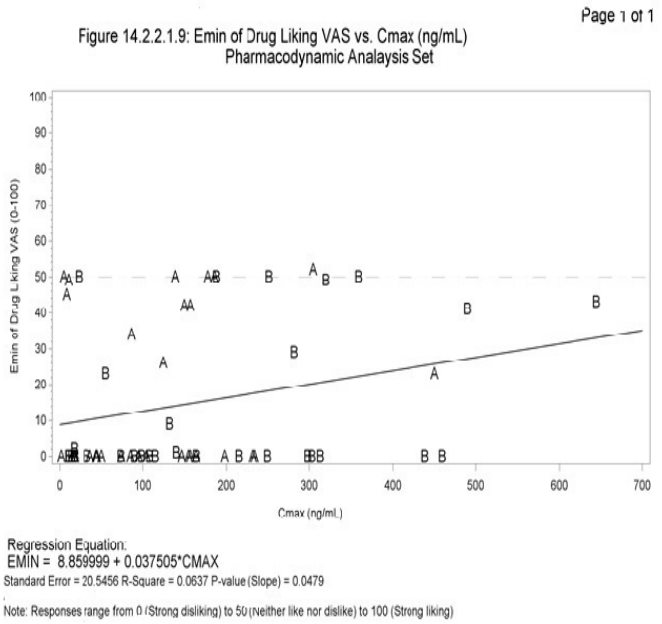
Influence of outliers on study results - further investigation/action plan

PK-PD Relationships

PD Scores versus PK Conc.



PD Endpoint versus PK Endpoint



Determine appropriate PK-PD relationship for HAL trials

Algorithme Pharma
AN ALTASCIENCES COMPANY

A Statistical Puzzle

Significant p-value when Median of Difference is 0
Wilcoxon Sign Rank Test

Table 14.2.2.7.3 ARCI Morphine Benzedrine Group (0-16): Treatment Comparisons of Emax
Non-Parametric Analysis
Pharmacodynamic Analysis Set

	Median of Intra-Subject Difference	Inter-Quartile Range for Difference	P-value
Effects			
Overall Treatment Effect	-----	-----	<.0001
Pairwise Comparisons			
Control Low Dose- Placebo (lactose tablets)	6.5	3.0, 11.5	<.0001
Control High Dose- Placebo (lactose tablets)	6.0	3.0, 11.0	<.0001
Test Low Dose- Control Low Dose	-4.0	-11.0, -1.0	<.0001
Test High Dose- Control Low Dose	-4.0	-10.0, -1.0	<.0001
Test Low Dose- Control High Dose	-6.0	-10.0, -1.0	<.0001
Test High Dose- Control High Dose	-4.0	-10.0, -1.0	<.0001
Test Low Dose- Placebo Test High Dose	0.0	0.0, 1.0	0.0327
Test High Dose- Placebo Test High Dose	0.0	0.0, 1.0	0.1411
Test Low Dose- Placebo (lactose tablets)	0.0	0.0, 1.0	0.0575
Test High Dose- Placebo (lactose tablets)	0.0	0.0, 1.0	0.0215
Placebo Test High Dose- Placebo (lactose blets)	0.0	0.0, 0.0	0.4961

The results are accurate☺ How can we explain this result?

Concluding Remarks

- Planning, analysis and producing a large number of tables and figures in a short time for a large complex multi-period crossover trial with 4 to 7 treatments and PK/PD/Safety assessments is a challenge
- A software tool to calculate the Sample Size for multi-period crossover trial will be helpful
- Need a non-parametric analysis method that can adjust the period, sequence and carryover effects
- Action on PD outliers for individual PD Scales need to be determined
- Need guidance on appropriate PK-PD relationship

Acknowledgment

Kerri Schoedel

Naama Levy-Cooperman

Beatrice Setnik

Marta Sokolowska