



# Statistical Graphics for Exploratory Review and Reporting in Clinical Trials

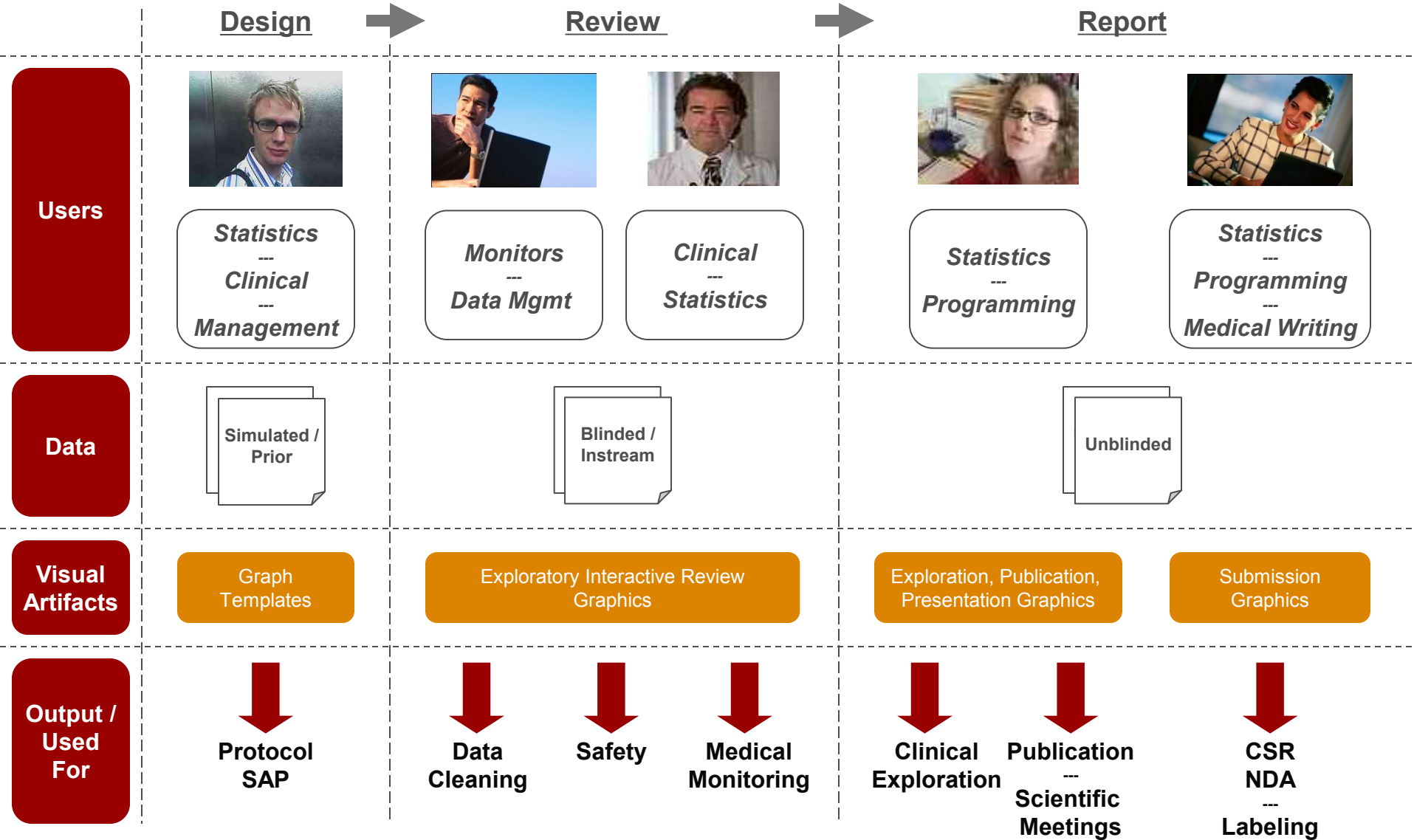
Michael O'Connell, PhD  
Clinical Practice  
TIBCO Software



# Acknowledgements

- **Ohad Amit, Peter Lane, Susan Duke, Mike Durante, Will Bushnell, GSK**
  - Safety graphics + graphics standardization implementation
- **Karina Stender, H. Lundbeck**
  - Graphics standardization implementation
- **Amy Xia, Kefei Zhou, Haijun Ma, Matt Austin, Amgen**
  - Safety graphics
- **Mat Soukup, George Rochester, FDA**
  - Safety graphics
- **Kye Gilder, Biogen IDEC**
  - Efficacy graphics
- **Andreas Krause, Actelion**
  - PKPD graphics
- **Michaela Jahn, Josh Haznedar, Xavier Logier, Roche**
  - Interactive exploratory graphics
- **Michael Merz, Novartis**
  - Interactive exploratory graphics
- **Harry Southworth, Ian Taylor, Paula Johansson, AstraZeneca**
  - Safety graphics and interactive exploratory graphics

# Clinical Graphics throughout Trial Lifecycle



# Report vs. Exploratory Review Graphics

## *Report*

- **Graph must be self-contained**
  - In-text figures should have an explanation in the caption
- **Graph must be documented**
  - Log file, time stamp
  - Source data and output file references
- **Examples**
  - NDA Submission
  - Scientific Publication
  - Clinical Study Report and Presentation
- **Color and Format**
  - Interpretable in black and white
  - Compatible with Microsoft Word
  - Resizable
- **Device**
  - WMF, PDF, PS

## *Review*

- **Graph may not be self-contained**
  - Interactive – brushing, drill-down and metadata
- **Graph may not be documented**
  - Data analyst produces to explore data
- **Examples**
  - Clinical data review by/with clinician
  - Viewing all data – data cleaning
  - Model diagnostics
- **Color and Format**
  - Few pre-defined rules
  - Just make it clear and easy to interpret
- **Device**
  - Interactive

*Many domains, functions benefit from statistical graphics*

- Trial Design
- Safety Data Analysis
  - Laboratory Measurements
  - Vitals Signs Measurements
  - Adverse Events
  - Patient Profiles
- Efficacy Data Analysis
- Trial Metrics and Operations

*O'Connell and Pietzko (2009), Statistical Graphics for Exploration  
Presentation, Publication and Submission in Clinical Development  
TIBCO Whitepaper (available on request)*

# Safety Data Analysis – Summary for Today

## □ Lots of data

- Many variables (labs, AE's, vitals, ...)

## □ Statistics / Analytics – FDA

- “P-values can provide some evidence of strength of the finding, but unless trials are designed for hypothesis testing (rarely the case), these **should be thought of as descriptive...**”
- “It should be appreciated that **exploratory analyses... are a critical and essential part of a safety evaluation....**”



# Safety Data Analysis – Summary for Today

- **Lots of data**
  - Many variables (labs, AE's, vitals, ...)
  
- **Statistics / Analytics**
  - Forget about p-values !!!
  - Testing multiplicity issue doesn't exist !!
  - Statistics: analyze data at subject level e.g. machine learning to prioritize AE/lab signals
  
- **Graphics – the key to success**
  - Targeted statistical graphics: AE's, labs, vitals at population and patient level
  - Interactive data review – patient profiles
  - Graphical Review – early and often !!



## □ **Labs**

- Which patients have changes in lab tests during trial
- Is there temporal causality of drug / conmed intake
- Liver labs and FDA DILI Guidance – Hy's Law

## ○ **Adverse Events**

- Review the TME's and DME's (e.g. cardio events)
- Are adverse events related to treatment or conmeds?
- Patterns of AE onset

## □ **Vitals and QT prolongation**

- Which patients have elevation in QTc during trial (FDA E14 Guidance)
- How do these subjects fare re. QTc and other safety issues

## □ **Combinations of data**

- Con meds, demographics, medical history, exposure
- Review subjects with AE and lab combinations e.g. rhabdomyolysis
- **Patient level analysis – Patient Profiling**

ClinicalReviewAE31Distn.dxp - TIBCO Spotfire

File Edit View Insert Tools Help

Demographics Disposition Labs out of range Lab Z-Scores **Lab Shift, Box** Labs All Timeline AE AE x Treatment QTc Change Patient Profile Lab Profile Labs x ULN ECG/Vitals Data Listing

Mark records below, then click to see Patient Details: [Profile](#) | [Labs](#) | [Labs x Upper Limit](#) | [ECG/Vitals](#)

View [liver panel](#) or [kidney panel](#), or use filter to select other lab tests.

### Labs - Shift Plot

### Box Plot - Lab Values vs. ULN

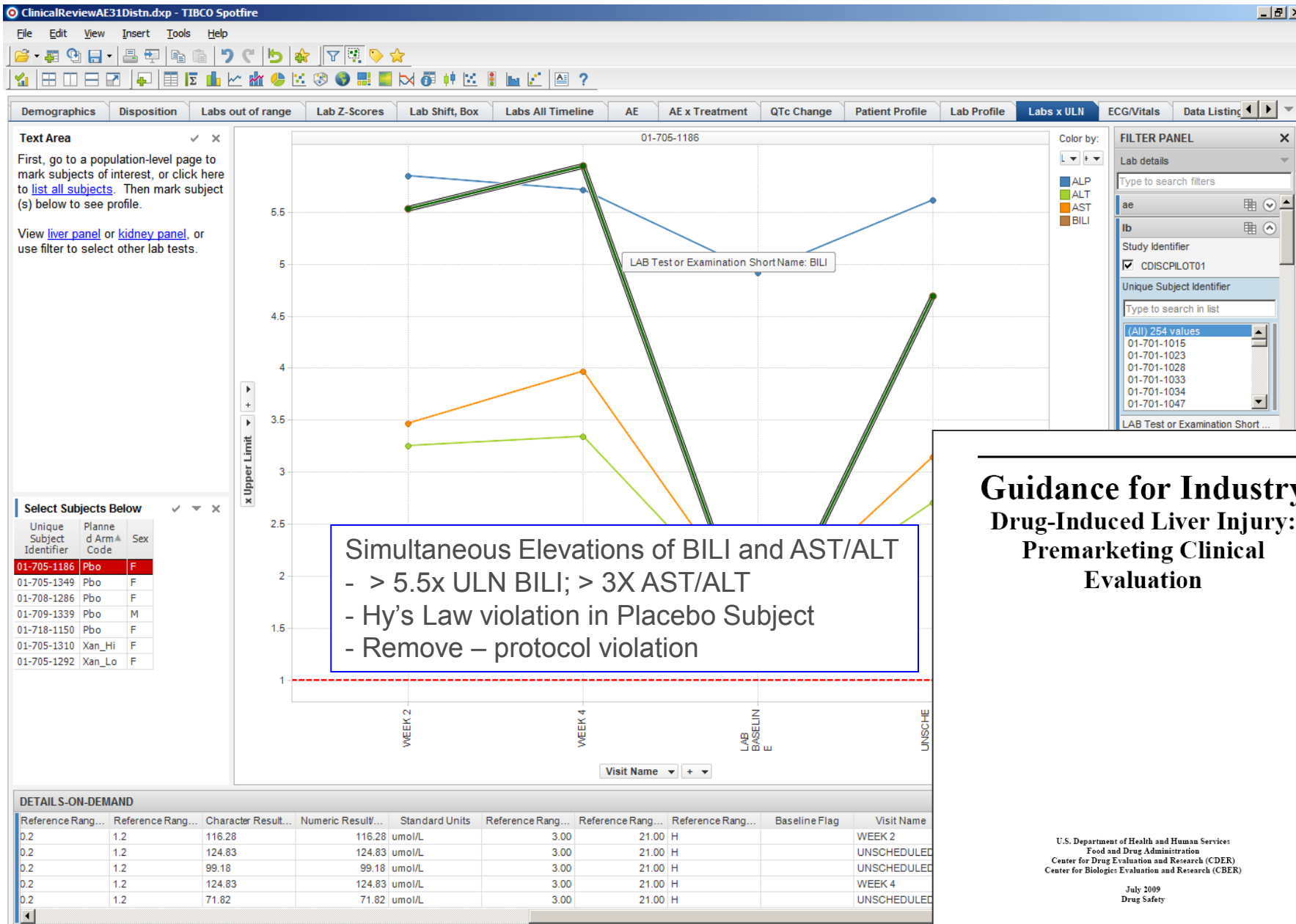
Highlight elevated labs (top left corners)  
Subjects saved to active subpopulation

Data table:  
Marking: Population Subje...  
Color by: (None)  
Reference points: All values, Median

### Details

Unique Subject Identifier	Visit Name	LAB Test or Examination Short Name	Numeric Result/Finding in Standard Units	Reference Range Lower Limit-Std Units	Reference Range Upper Limit-Std Units	Z-score
01-705-1186	LAB BASELINE	ALT	50.00	6.00	32.00	3.00
01-705-1186	WEEK 2	ALT	104.00	6.00	32.00	8.18
01-705-1186	UNSCHEDULED	ALT	95.00	6.00	32.00	7.32
01-705-1186	UNSCHEDULED	ALT	92.00	6.00	32.00	7.03
01-705-1186	WEEK 4	ALT	107.00	6.00	32.00	8.47
01-705-1186	UNSCHEDULED	ALT	73.00	6.00	32.00	5.21
01-705-1186	LAB BASELINE	AST	54.00	9.00	34.00	3.12
01-705-1186	WEEK 2	AST	118.00	9.00	34.00	9.64

7266 of 59580 rows | 106 marked | 25 columns | lb



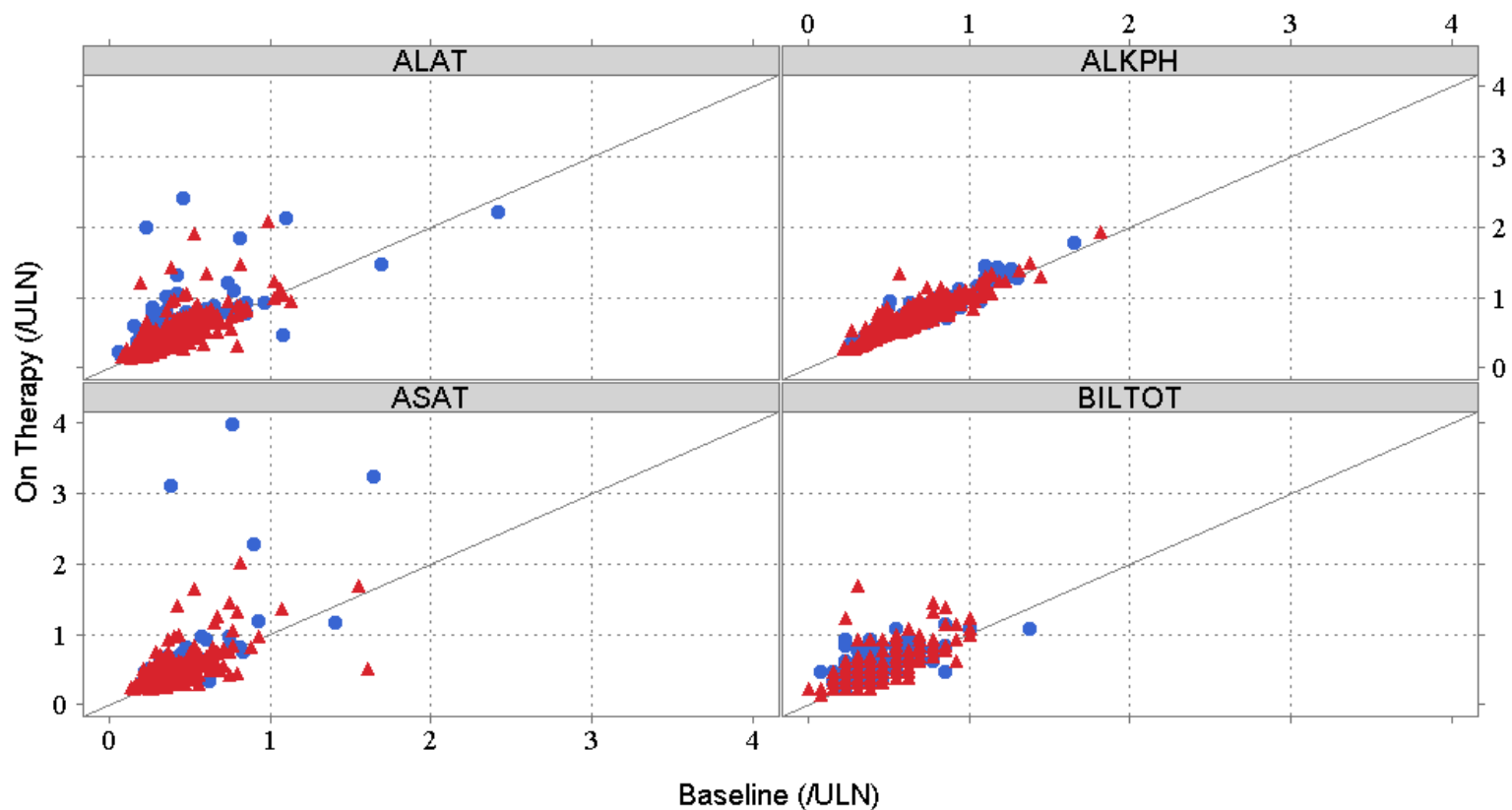
## Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

July 2009  
Drug Safety

Protocol: AL-303-SC

## Liver Lab Shift Plot

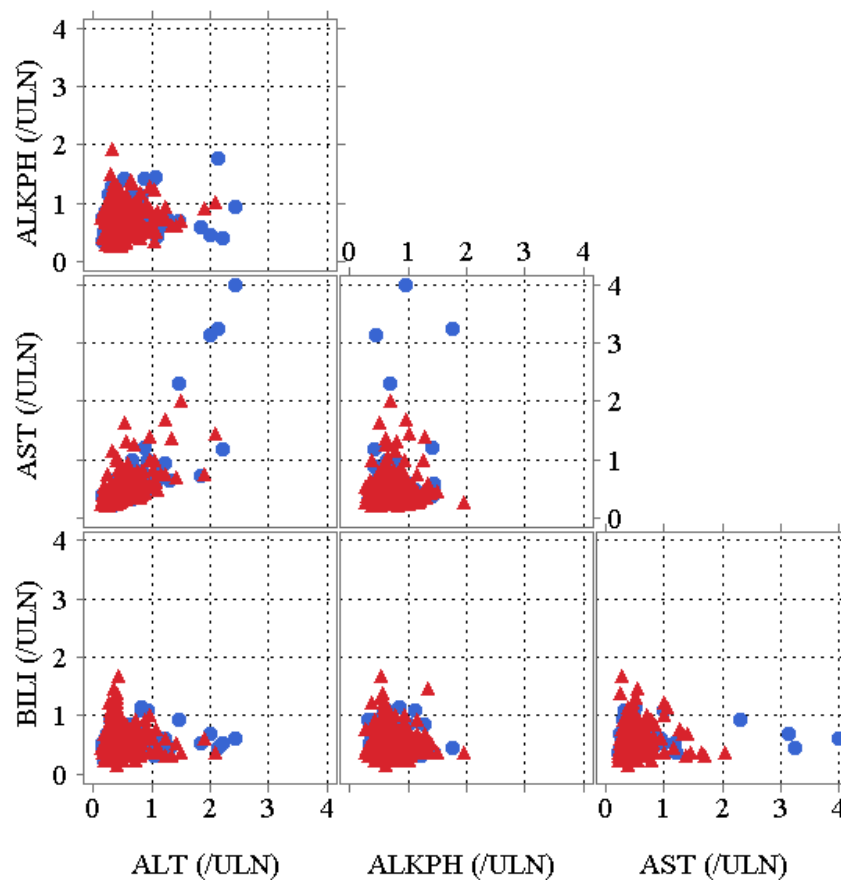


Treatment Group  
Placebo ●  
Low Dose ▲

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User: M OConnell  
Date: May 15 2009

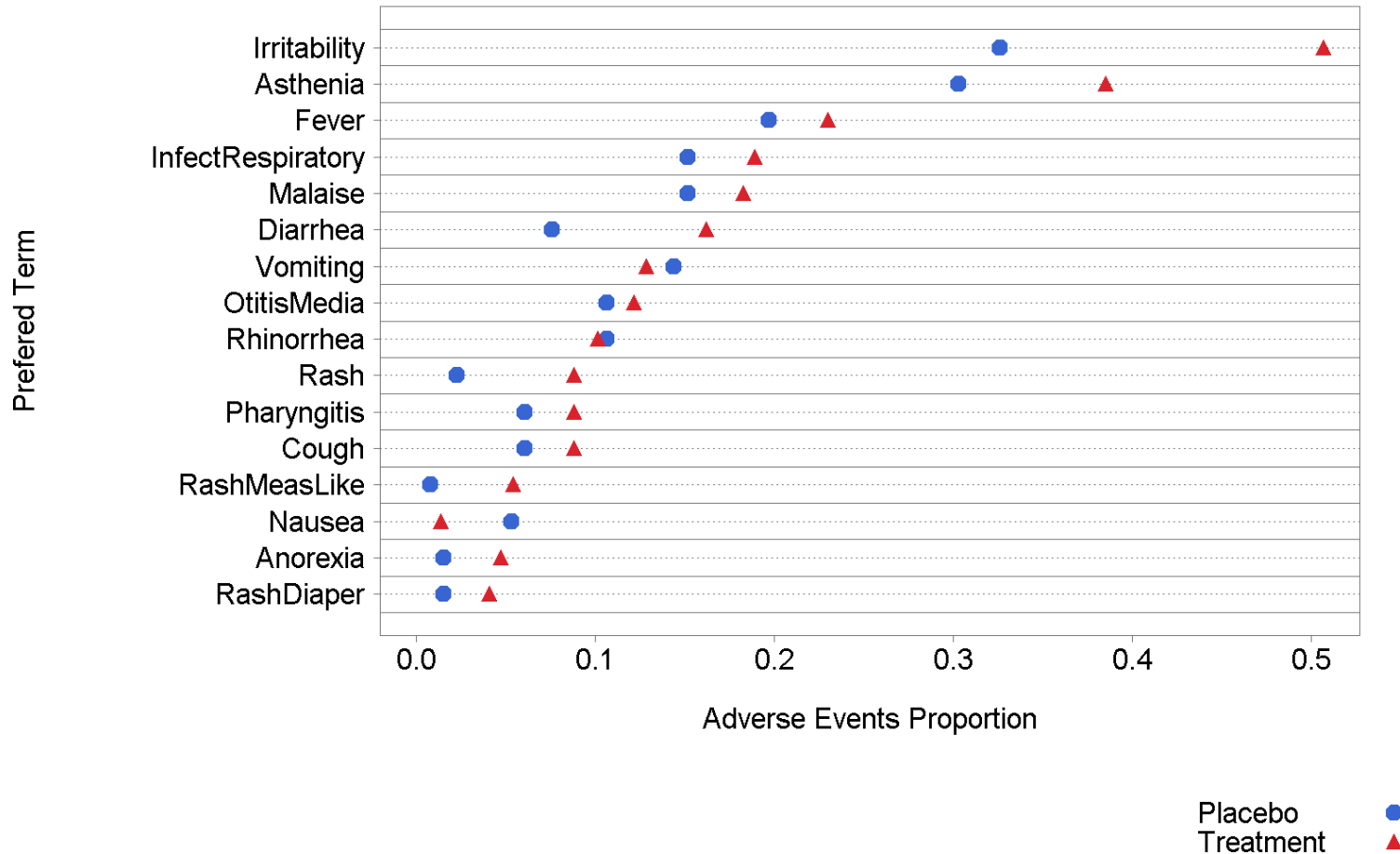
lft5.unstack.endpt.csv

Matrix Display of LFT (/ULN)



DRUG A ●  
DRUG B ▲

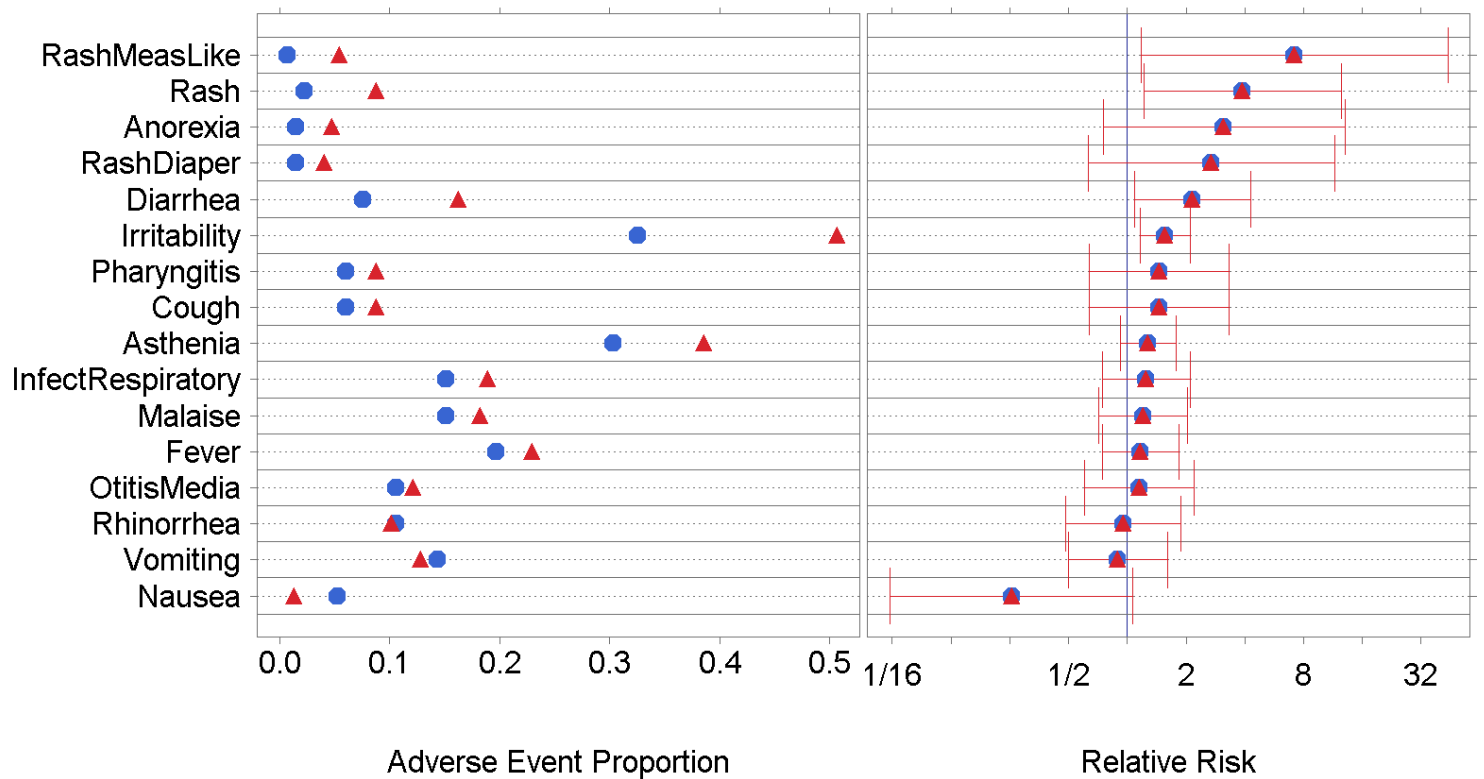
Adverse Events Rates: Treatment vs Control



Data: <http://PCKPIETZKO01197:8080/PlusServer/webdav/tscg/files/DataSources/Users/kpietzko/heyseDataFig1.xls>  
 Author: kpietzko  
 Last Modified: 2009-08-21T09:28:37.2812500+02:00  
 Version: 2.0.3; Validation: Not Validated

Data: Mehrotra and Heyse

Adverse Events sorted by Relative Risk

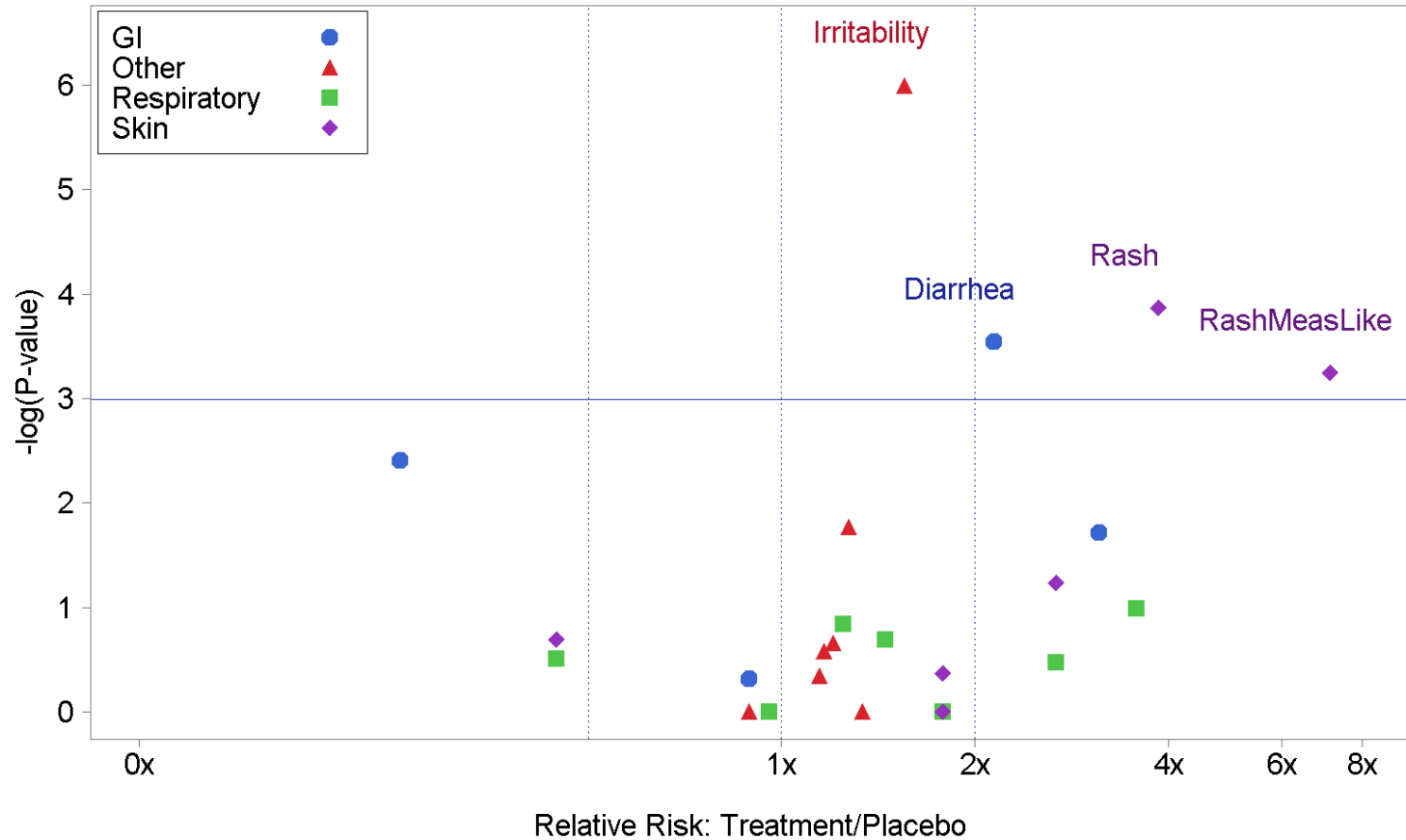


Placebo (N=132) ● —  
 Treatment (N=148) ▲ —

Data: [http://PCKPIETZKO01197:8080/SplusServer/webdav/tscg/files/DataSources/Examples/double\\_dot\\_data.csv](http://PCKPIETZKO01197:8080/SplusServer/webdav/tscg/files/DataSources/Examples/double_dot_data.csv)  
 Author: kpietzko  
 Last Modified: 2009-08-20T10:08:38.2771152+02:00  
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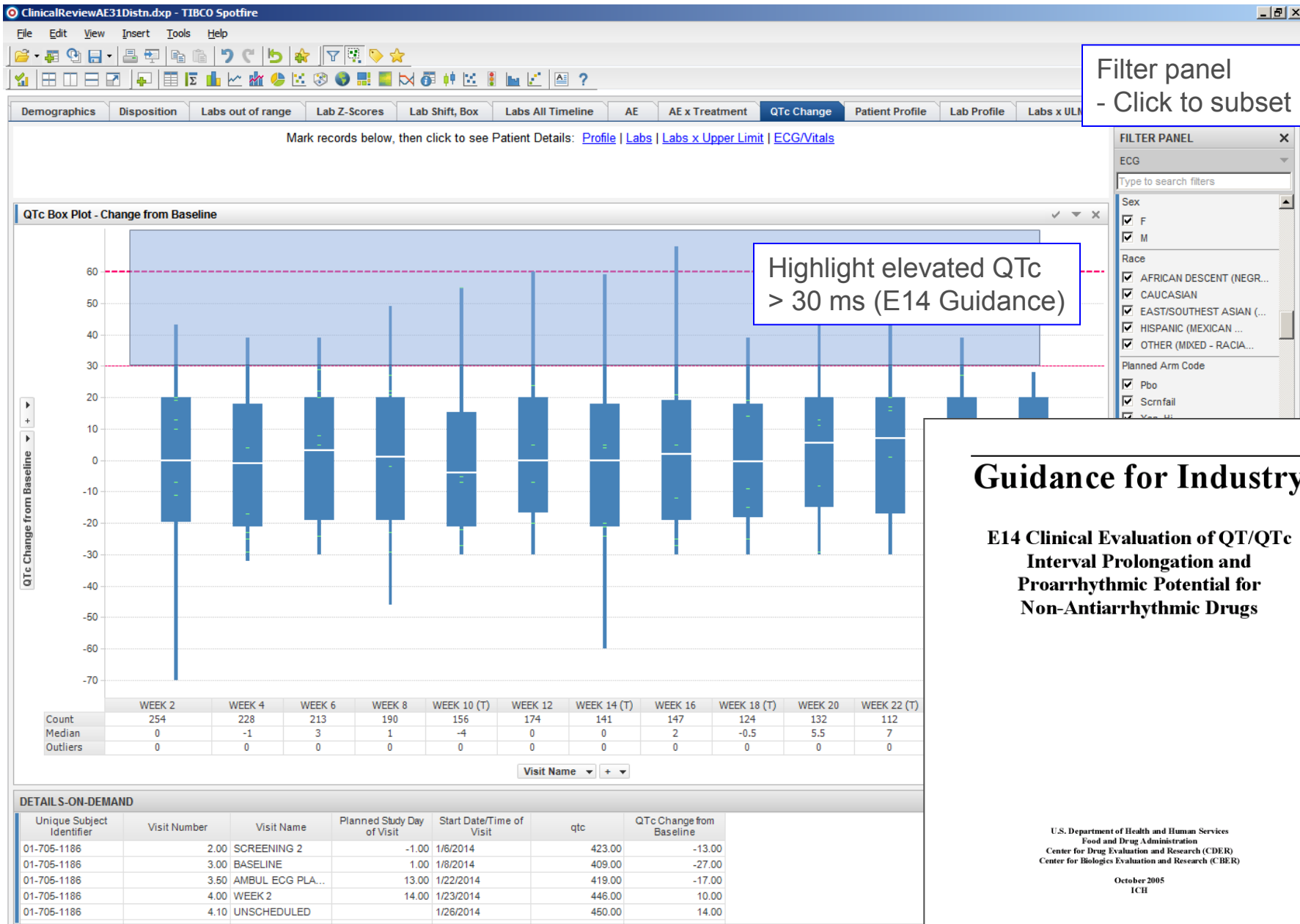
Data: Mehrotra and Heyse  
 Graph: Amit, Lane, Heiberger

## Risk Plot of Adverse Events Rates



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Author: kpietzko  
Last Modified: 2009-08-21T09:26:24.6093750+02:00  
Version: 2.0.3; Validation: Not Validated

Data: Mehrotra and Heyse



Filter panel  
- Click to subset

## Guidance for Industry

### E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

October 2005  
ICH

ClinicalReviewAE31Distn.dxp - TIBCO Spotfire

File Edit View Insert Tools Help

Demographics Disposition Labs out of range Lab Z-Scores Lab Shift, Box Labs All Timeline AE AE x Treatment QTc Change Patient Profile Lab Profile Labs x ULN ECG/Vitals Data Listing

First, go to a population-level page to mark subjects of interest, or click here to [list all subjects](#). Then mark subject (s) below to see profile.

**ECG: QTc**

01-701-1180

Avg(qtc)

Subject has elevated delta (>30 ms) and elevated QTc (>500 ms)

**Select Subjects Below**

Unique Subject Identifier	Planned Arm Code	Sex
01-701-1363	Pbo	F
01-703-1299	Pbo	F
01-704-1010	Pbo	M
01-704-1388	Pbo	M
01-706-1041	Pbo	F
01-708-1087	Pbo	F
01-708-1316	Pbo	F
01-709-1088	Pbo	M
01-713-1179	Pbo	F
01-716-1160	Pbo	F
01-717-1344	Pbo	F
01-718-1139	Pbo	M
01-718-1150	Pbo	F
01-701-1034	Xan_Hi	F
<b>01-701-1180</b>	<b>Xan_Hi</b>	<b>M</b>
01-701-1275	Xan_Hi	M
01-701-1383	Xan_Hi	F
01-703-1258	Xan_Hi	F
01-708-1406	Xan_Hi	F
01-709-1099	Xan_Hi	F
01-701-1294	Xan_Lo	M
01-703-1086	Xan_Lo	M
01-705-1431	Xan_Lo	F
01-716-1167	Xan_Lo	M

**Vitals**

01-701-1180

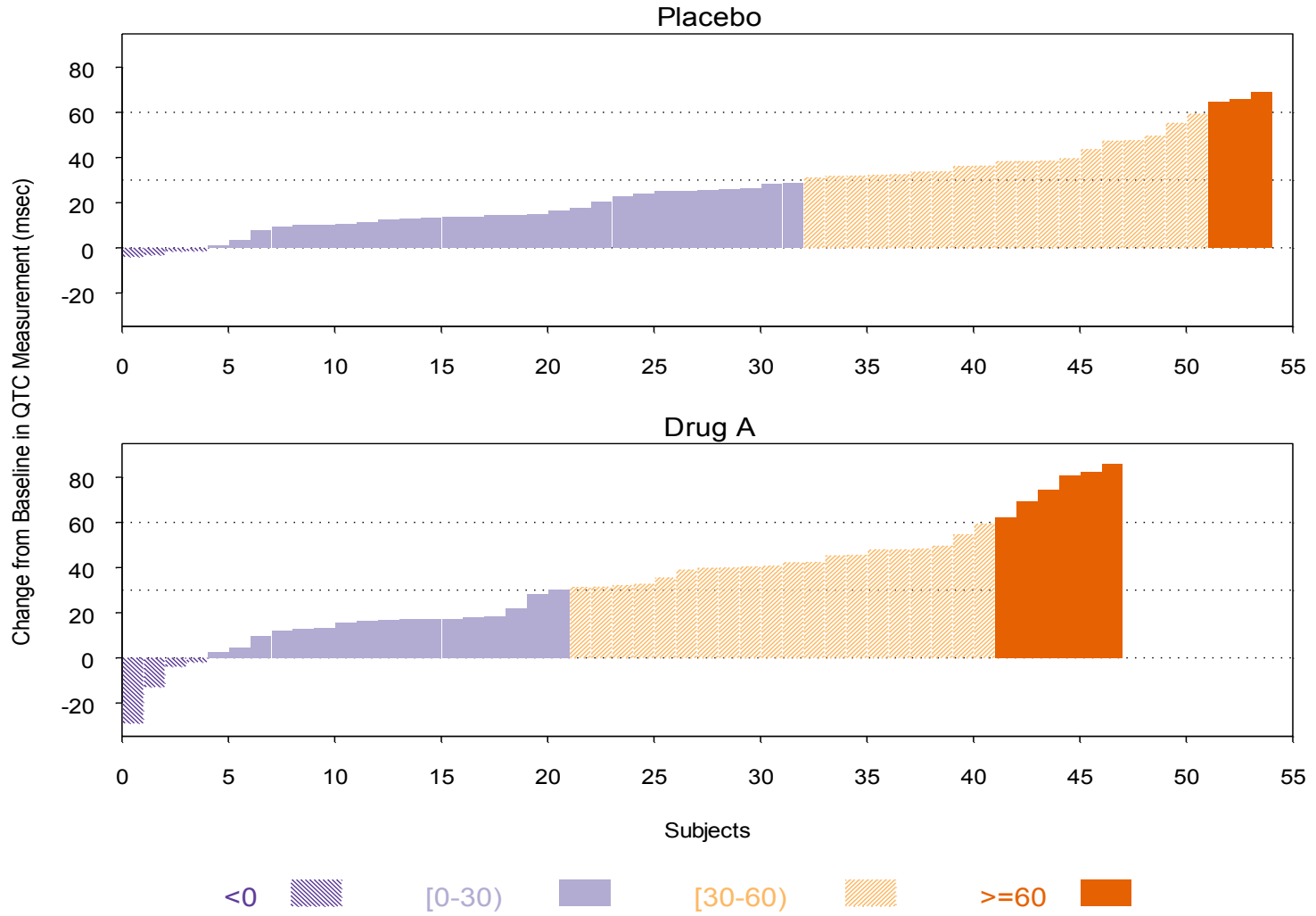
Avg(Numeric Result/Finding in Standard Units)

Color by: DIABP, SYSBP, WEIGHT

Visit Name

306 of 306 rows | 1 marked | 16 columns | dm

Figure X  
Change in QTc measurement at 12 Weeks from Baseline



ClinicalReviewDemoSep09.dxp - TIBCO Spotfire

File Edit View Insert Tools Help

Demograph Labs out of range Lab Z-scores Labs vs ULN Labs Timeline AE QTC change **Patient Profile** Labs Labs x ULN ECG/Vit

First, go to a population-level page to mark subjects of interest, or click here to [list all subjects](#). Then mark subject(s) below to see profile.

Select Subje... ✓ ▾ ×

USUBJID	TRTGRP	SEX
31-351-2254	TstDs1	F
31-351-2316	Placebo	M
31-351-2328	Placebo	M
31-351-2349	TstDs1	M

Web Details ×

Make a selection:

- [Tabular Patient Profile](#)
- [Graphical Patient Profile](#)

**Patient Profile** ✓ ▾ ×

event\_type

- conmed
  - OXYCONTIN
  - OXYCODONE
  - NEURONTIN
  - MIRALAX
  - METOPROLOL
  - MAGNESIUM CITRATE
  - FLEET ENEMA
  - DULCOLAX
  - AMBIEN CR
  - ALEVE
- ae
  - SECRETION DISCHARGE
  - PNEUMONIA
  - NASAL MUCOSA BIOPSY
  - MUSCULAR WEAKNESS
  - ERYTHEMA FACIAL
  - COUGH
- lab
  - APPLICATION SITE REDN...
  - APPLICATION SITE ITCHING
  - APPLICATION SITE BURNI...
  - BILI
  - AST
  - ALT
  - ALP

day\_in\_study

2254

FILTER PANEL ×

Patient Profile

Type to search filters

patient\_profile

event\_type

- lab
- ae
- conmed
- dose

day\_in\_study

-750 324

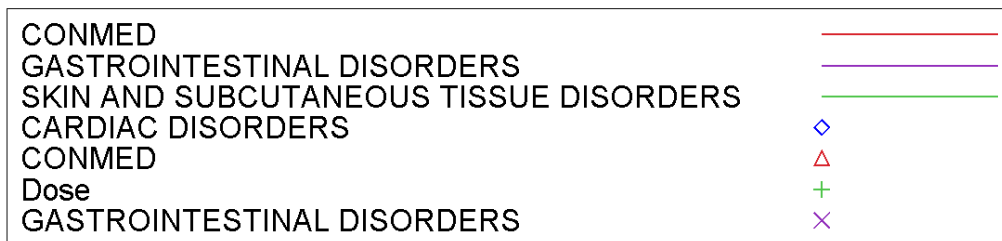
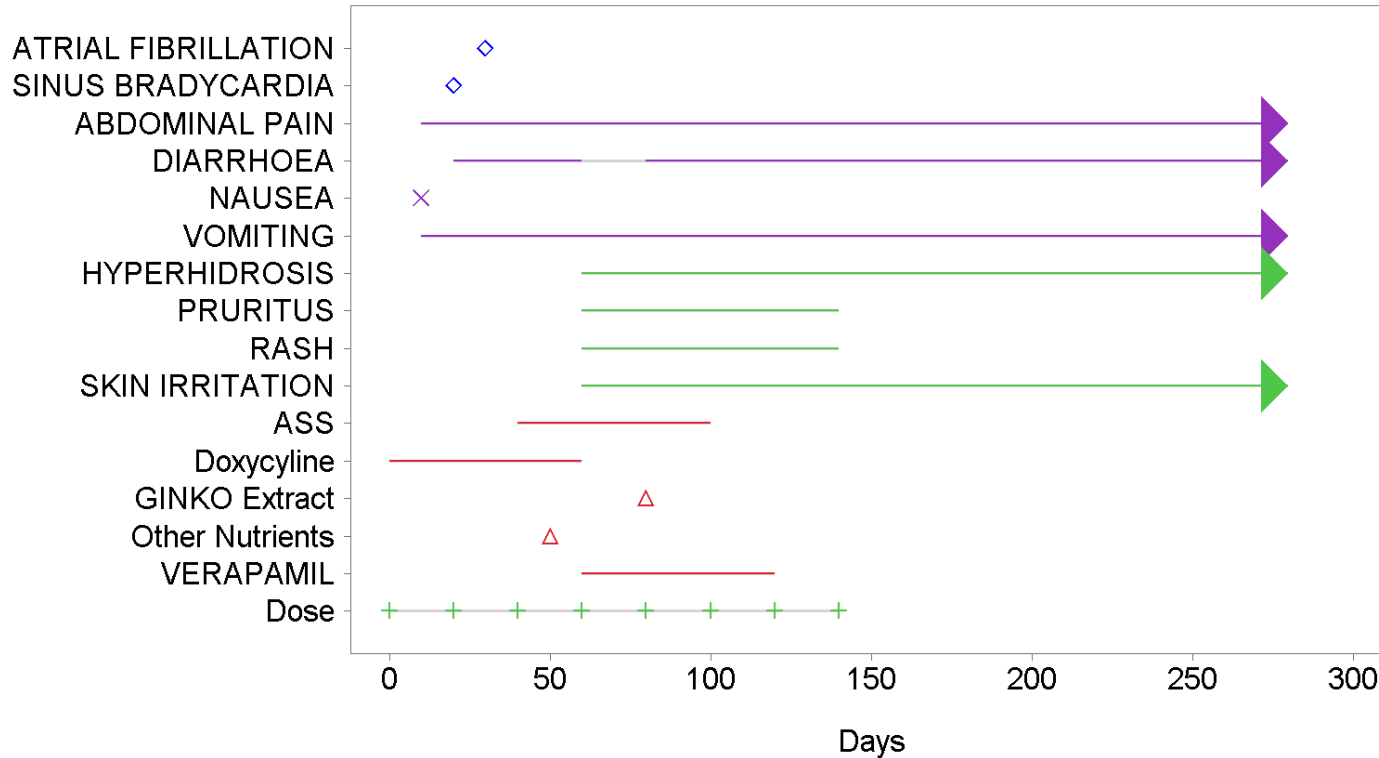
Include empty values

LBTESTCD

- ALB
- ALP
- ALT
- ANISO
- AST
- BASO
- BILI
- BUN
- CA
- CHOL
- CK
- CL
- CREAT
- EOS

Some filters are hidden. [Show all](#)

## Patient Profile: SubjId: 000112



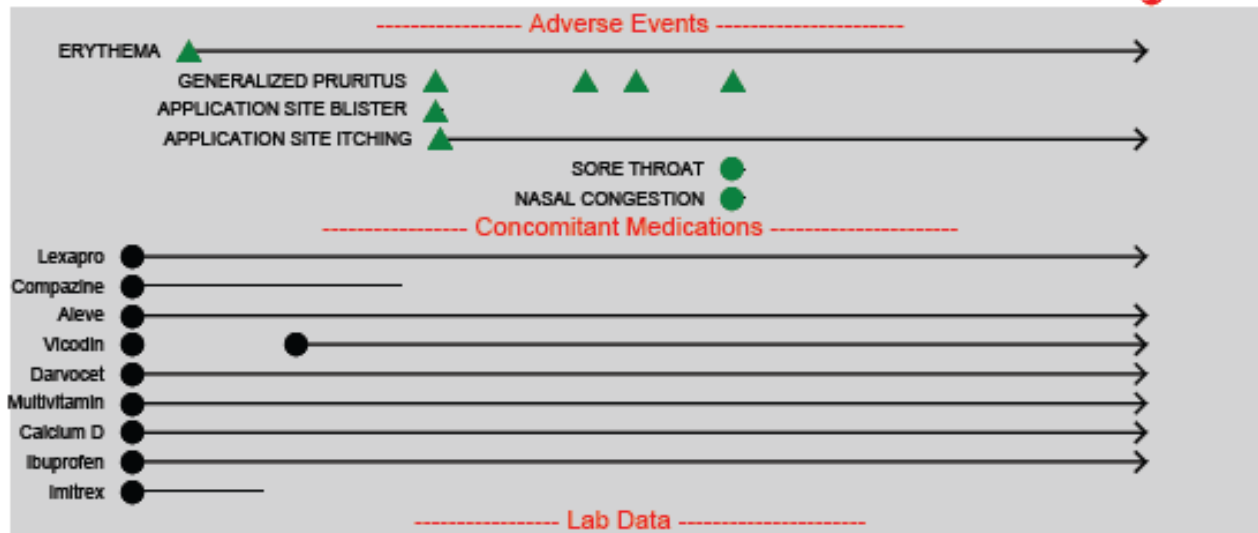
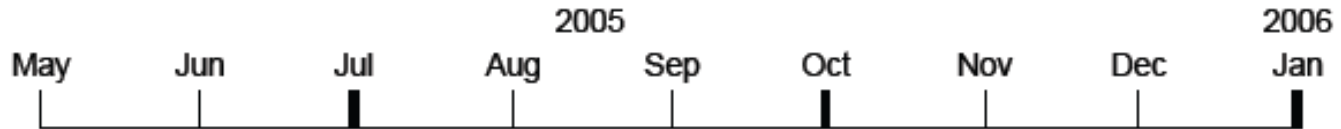
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Author: kpietzko

Last Modified: 2009-08-23T12:54:02.2968750+02:00

Version: 2.0.1; Validation: Not Validated

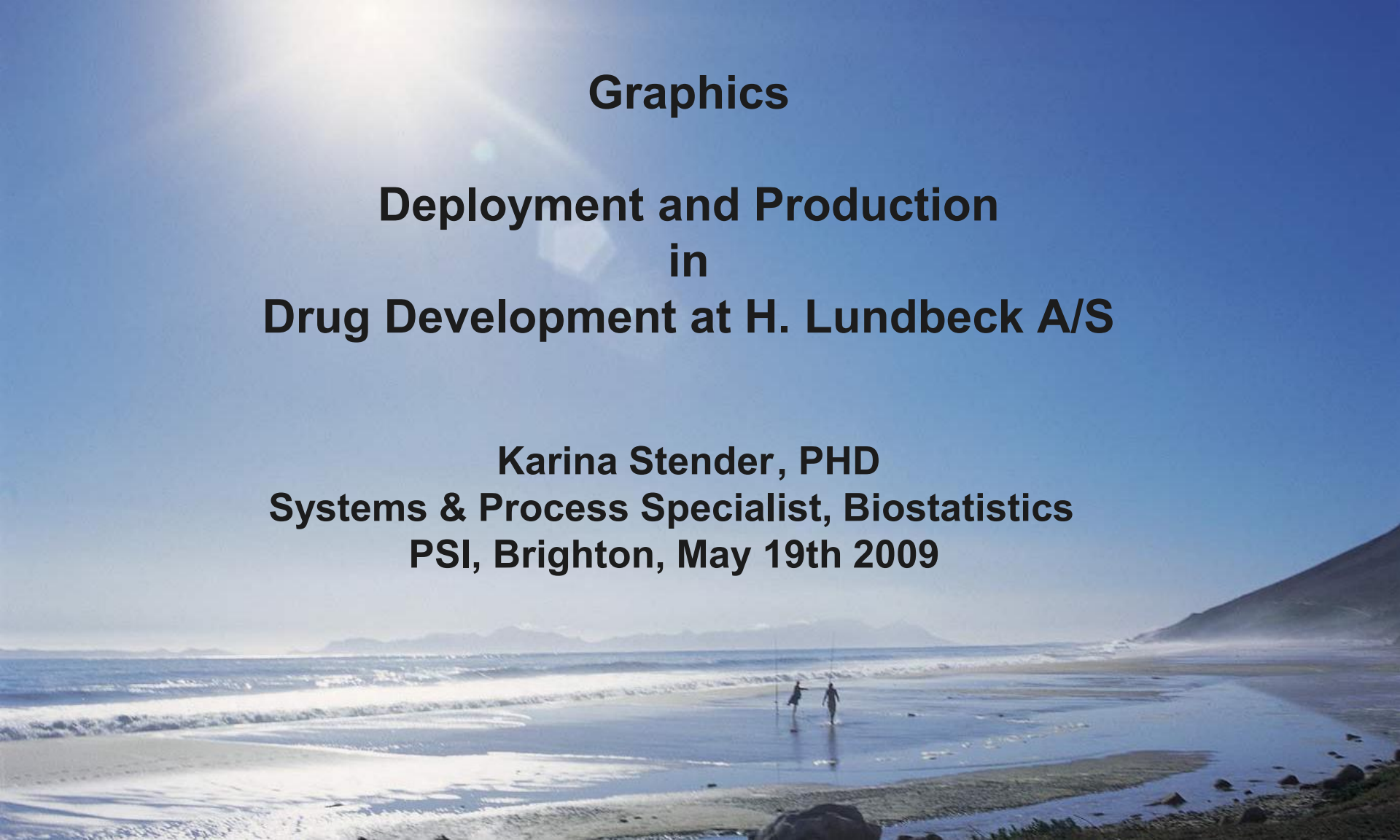
Study: Prostinol Subject: 2349  
 Birth Date/Sex: 06/10/1937/Male Trt:TstDs1



----- Lab Data -----

ALB	43	42	42	41	43	41	42	39	43	40
ALP	56	54	49	48	49	53	67	50	54	52
ALT	16	24	17	14	18	14	15	11	18	15
AST	19	21	16	19	18	17	17	16	20	19
BASO	0.06	0.05	0.06	0.07	0.08	0.06	0.08	0.04	0.06	0.06
BILI	6.84	8.55	10.3	8.55	8.55	6.84	6.84	5.13	10.3	8.55
BUN	7.5	8.57	8.21	7.5	7.5	7.85	7.5	6.78	6.43	6.78
CA	2.32	2.35	2.27	2.22	2.35	2.27	2.25	2.17	2.2	2.32
CHOL	6.23	6.13	5.77	5.56	6.15	5.66	5.72	5.38	5.84	5.3
CK	96	84	86	126	88	63	77	82	98	86
CL	103	104	103	106	100	102	103	108	103	108
CREAT	124	133	133	133	133	133	133	133	124	141
EOS	0.08	0.08	0.3	0.39	0.89	0.87	0.44	0.56	0.21	0.3
GGT	18	21	18	16	19	19	20	16	20	16
GLUC	5.16	5	5.38	3.72	4.94	5.94	5	4.33	5.33	4.94

Graph: Austin



# Graphics

## Deployment and Production in Drug Development at H. Lundbeck A/S

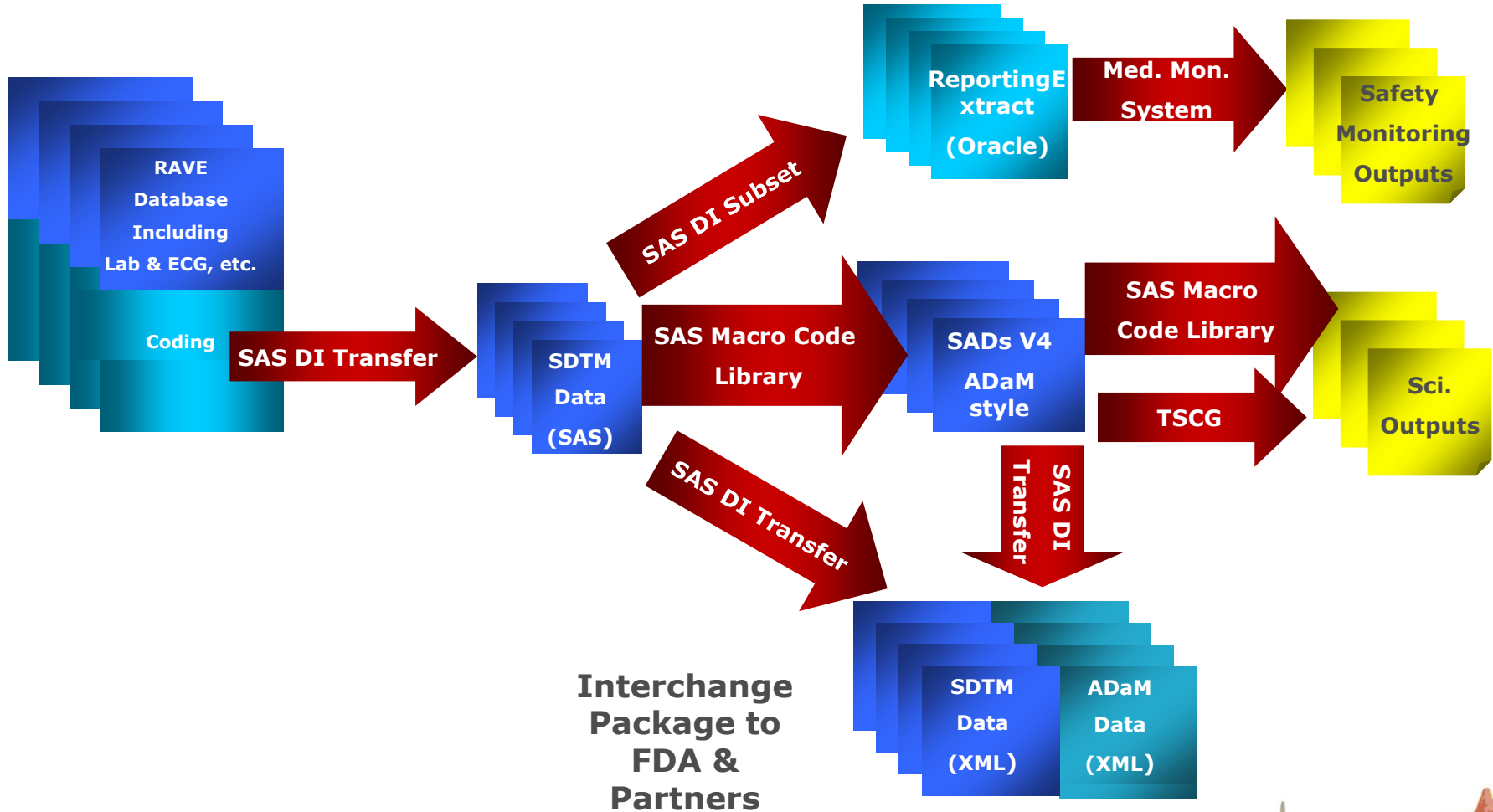
**Karina Stender, PHD**  
**Systems & Process Specialist, Biostatistics**  
**PSI, Brighton, May 19th 2009**

Karina Stender, PhD, System & Process Specialist, Biostatistics  
H. Lundbeck A/S





# Lundbeck Case Study - Data Flow & Reporting Systems Implemented Solution





**Susan Duke, MS, MS**

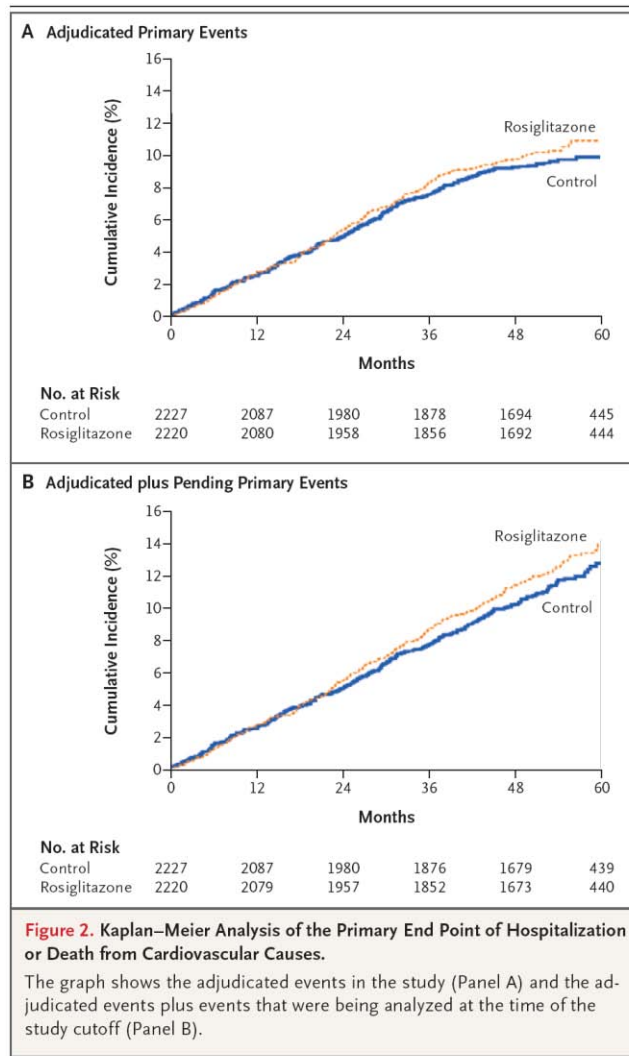
**Associate Director,  
Biostatistics Development Partners**

**Sept 17 2008**

**ASA FDA/Industry Workshop**



# Graphics Standardization – GSK Case Study – Avandia



## Quote from Avandia Statistics Mgr

For the RECORD (Avandia) interim analysis, we had less than 24 hours to unblind the trial and get a presentation together for a senior management briefing.

Within this timeframe, using S-PLUS, we were able to produce highly impactful Kaplan-Meier and Forest plots, for a number of endpoints.

The plots were very well received and I believe helped the group understand and interpret the data expeditiously.

I doubt we could have developed the SAS code in time, not to mention to the same quality and level of impact. They were easy to export into word, powerpoint, pdf.

I thought someone should know that efforts to roll out S-PLUS have been i) appreciated and ii) worthwhile

# ASA Statistical Graphics (and Computing) Newsletter



The screenshot shows a web browser window with the address bar containing <http://stat-computing.org/newsletter/>. The page features the ASA logo on the left and navigation links for [ Computing, Graphics ], [ Awards, Data expo, Video library ], and [ Events, News, Newsletter ] on the right. A search box is also present. The main content area includes a 'Home' link, the title 'SCGN Newsletter', and a paragraph explaining the newsletter's distribution to members of the Statistical Computing and Statistical Graphics Sections of the ASA. Below this are sections for 'Editorial Staff', 'Online Issues', and 'Featured articles:'. A 'Recent issues' sidebar on the right lists several past issues with their dates.

ASA Sections on:

[Statistical Computing](#)  
[Statistical Graphics](#)

[ [Computing](#), [Graphics](#) ]  
[ [Awards](#), [Data expo](#), [Video library](#) ]  
[ [Events](#), [News](#), [Newsletter](#) ]

[Home](#)

## SCGN Newsletter

The Computing and Graphics Newsletter is distributed to members of the [Statistical Computing](#) and [Statistical Graphics](#) Sections of the [ASA](#). Their annual dues assist section activities. If you are an ASA member, but do not belong to either of these Sections, please consider joining. If you are not an ASA member, but find the articles in the Newsletter interesting, you might want to give our [organization a look](#).

**Editorial Staff**

The Newsletter is produced by two *volunteer* editors, one from each of the Computing and Graphics Sections, with articles from both ASA members and non-members. Our current editors are Nicholas Lewin-Koh (Computing) and [Andreas Krause](#) (Graphics). We are eager to hear both from people who receive the newsletter regularly as well as interested visitors who have examined our site. Consider giving us feedback about how we can improve this service.

**Online Issues**

As a service to our members, we make PDF versions of the complete Newsletter available for downloading. Even if you are not a member, feel free to browse through our collection. If you like what you see, consider joining our sections!

[Volume 20, Number 1. July 2009](#)

Featured articles:

[Consider Librating the news from the burden of time](#)

**Recent issues**

- [Volume 20, Number 1.](#)  
July 2009
- [Volume 19, Number 2.](#)  
December 2008
- [Volume 19, Number 1.](#)  
July 2008
- [Volume 18, Number 2.](#)  
December 2007
- [Volume 18, Number 1.](#)  
June 2007

- **Statistical Graphics are at the core in the analysis and interpretation of clinical / safety data**
  - Design – compare designs, understand potential trial behavior
  - Exploratory – understand the data, cleaning and outliers
  - Review – all components of population and patient level data
  - Submission – clinical study reports
  - Presentation, Publication – scientific and marketing applications
  
- **Standardization of Clinical Graphics – incorporating statistical graphics principles – is key**
  - Same graphs in reports and exploratory data browsing
  - Graphical language across organizations and industry
  
- **This is widely recognized by industry and the FDA**

# TIBCO Graphical Software for Clinical Development

## □ TIBCO Spotfire - Clinical

- Exploratory Review, Operations, Safety
- Spotfire Clinical Templates
- S+/R Integration

## □ TIBCO Spotfire S+

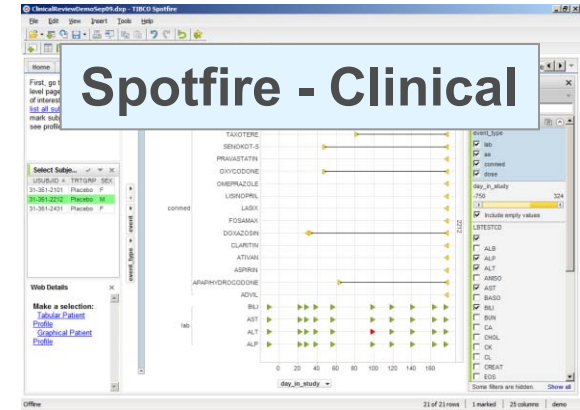
- Package system, graphics, big data, eclipse
- Graphics focus

## □ S+ Clinical Graphics

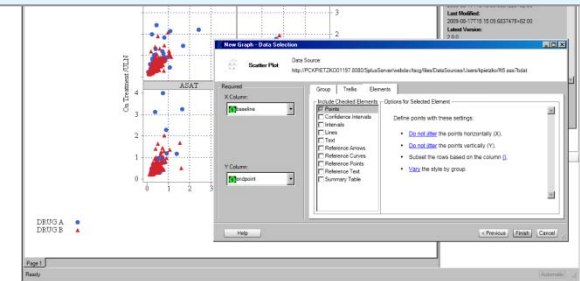
- Clinical Graphics (Report Graphics)
- S+ Engine

## □ Integration of Products in Motion

- TS and S+
- TS and S+CG
- S+ and S+CG



## S+ / Clinical Graphics



TIBCO Spotfire S+® 8.1 for Windows

Rev Date: Tue Nov 04 22:13:49 2008 Build: M8622

S+®

Spotfire®

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TIBCO Spotfire S+

# Questions

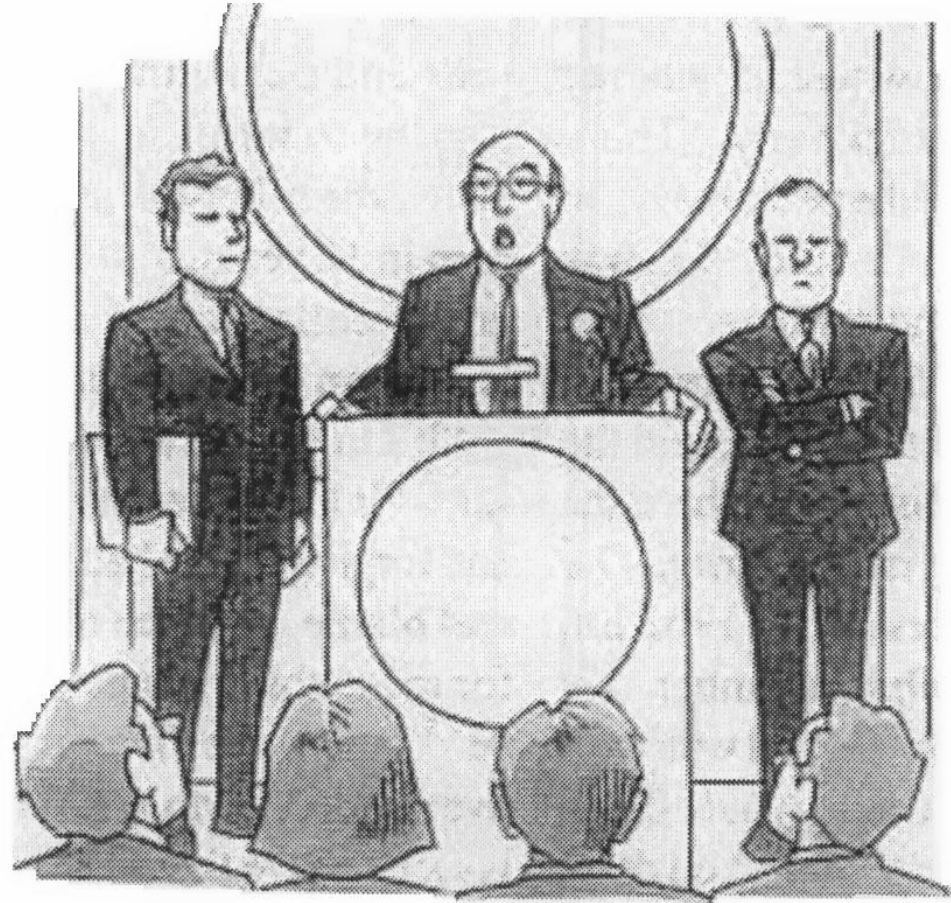
Michael O'Connell, Ph.D.

Sr Director, Analytics

TIBCO Software

[moconnel@tibco.com](mailto:moconnel@tibco.com)

+1 919 7401560



**"I believe I evaded that question earlier."**

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