



eBESTTM
REPORTS

Innovative reporting engines

Overview

from

StatFinn Ltd



Benefits

- **Saving resources:** → experts released for more demanding tasks than report writing.
- **Saving time:** 24h delivery from data received → Getting your report done faster will shorten the time of drug development and hence will bring your drugs earlier to the market
- **Your Profit:** Drug on market can generate revenue upto 10m/day → getting your drug to the market earlier does not only give you better change of being the market lead but also gives you millions of \$€.



Facts

- eBESTreports is a first-in-market reporting tool that shortens the reporting time from the average of 30 days to 24 hours.
- eBESTreports is a cloud service: the user needs only an Internet access and a browser (also available as traditional CRO service)
- eBESTreports portal is intuitive and easy to use.



Facts

- The user can upload the data into the secure portal any time they want and active the report engine. Within 24 hours the full report with all the appendices according to EMA/FDA guidelines is downloadable from the portal.
- eBESTreports can be tailored to use specific reporting templates and logos etc. from sponsors / clients can be implemented to make it look exactly like your report.



QA & Security

- Full audit trail from the data upload to report delivery in version controlled SAS environment.
- Our tools and environment are compliant with FDA 21 CFR part 11 and are also corresponding to GCP and FDA's Guidance of Computerized Systems Used in Clinical Trials.
- Performance of the web-portal has been validated with process including Installation, Operational and Performance Qualification test according to validation of computerized systems. No performance problems have been recorded.



QA & Security

- Data transfer happens through SSL secured web portal with VPN connection between clients system and our server through two firewalls. On our server data for each client is stored on dedicated partition. The final report will be distributed to the client via this same secured portal.
- After the report comes out from our eBESTreports engine it is carefully reviewed by our expert.
- Only after this review experts will release the documents: Report (Stat & PK summary), Appendix 1 (descriptive summary tables and graphs) and Appendix 2 (Individual data, graphs and detailed calculations).

The Portal

[DASHBOARD](#)[EDIT USERS](#)[ABOUT ePRODUCTS](#)[LOGOUT](#)

Welcome **NOVARTIS - MATTI MEIKÄLÄINEN**

MY LATEST STUDIES

[SEARCH](#)

Last created or edited

Project Name	Study Name(?)	Type	Created by	Status
Laskentamolekyyli 1	E-V45	Prod1	Tero Raitanen	1 2 3 4
Laskentamolekyyli 2	HUU-HAA	Prod2	Mrs. Winters	1 2 3 4

[OPEN SELECTED STUDY](#)

MY PROJECTS

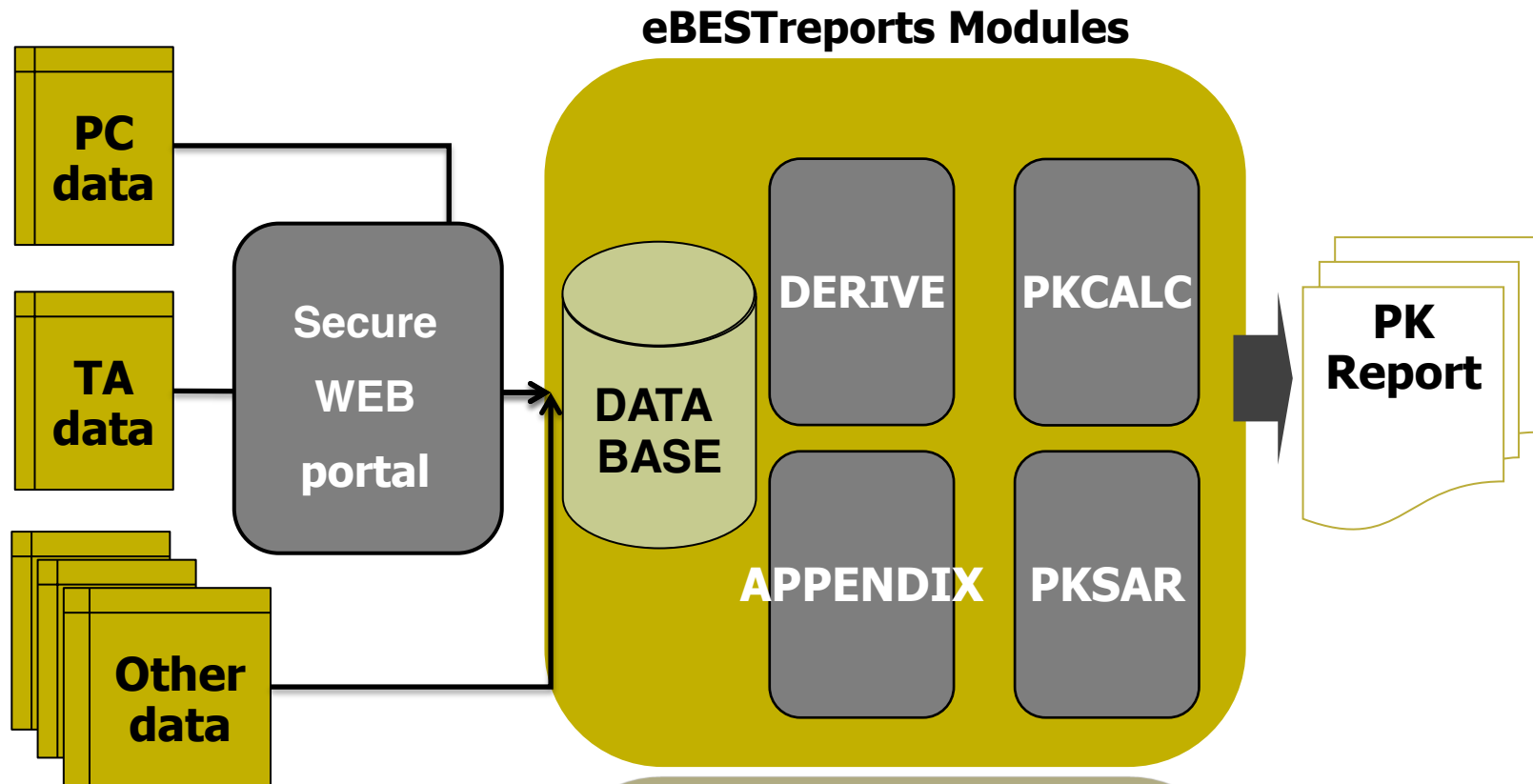
[SEARCH](#)

Last used projects

Project Name	Contact	Nro of Studies	
Laskentamolekyyli 1	Tero Raitanen	4	EDIT
Laskentamolekyyli 2	Jaska Jokunen	5	EDIT

[NEW STUDY TO SELECTED PROJECT](#)[CREATE A NEW STUDY](#)

PROCESS



**Compliant with FDA CFR part 11 and
Guidance of Computerized Systems Used in Clinical Trials**



Report Types

eBESTreports currently available :

- **eBESTbio** = *PK report for bio-equivalence study with PK calculations, analysis according to regulatory guidelines, all appendices, and bio-equivalence claim statement. In 24 hours from data upload. .*
- **eBESTfood** = *PK report for food interaction study with PK calculations, analysis according to regulatory guidelines, and all appendices. In 24 hours from data upload.*
- **eBESTdrug** = *PK report for drug interaction study with PK calculations, analysis according to regulatory guidelines, and all appendices. In 24 hours from data upload.*
- **eBESTpk** = *PK report for any pharmacokinetic study with PK calculations, tables and graphs according to regulatory guidelines. In 24 hours from the data upload.*
- **eBESTgi** = *Glycemic Index report for glycemic profile studies with GI calculations, tables and graphs according to regulatory guidelines.. In 24 hours from the data upload.*
- In the pipeline = **eBESTtox, eBESTab, eBESTpro**



eBESTreports STEPS

User uploads concentration data and sets related metadata

User activates eBESTreports engine

eBESTreports calculates pharmacokinetic parameters

eBESTreports executes analyses and creates reports

eBESTreports generates appendices

eBESTreports creates pharmacokinetic analysis report

Report is reviewed by our experts

eBESTreports sends User report-ready email

User downloads report



eBESTTM
REPORTS

Innovative reporting engines

PK calculation, Statistical Analyses & Reports

from

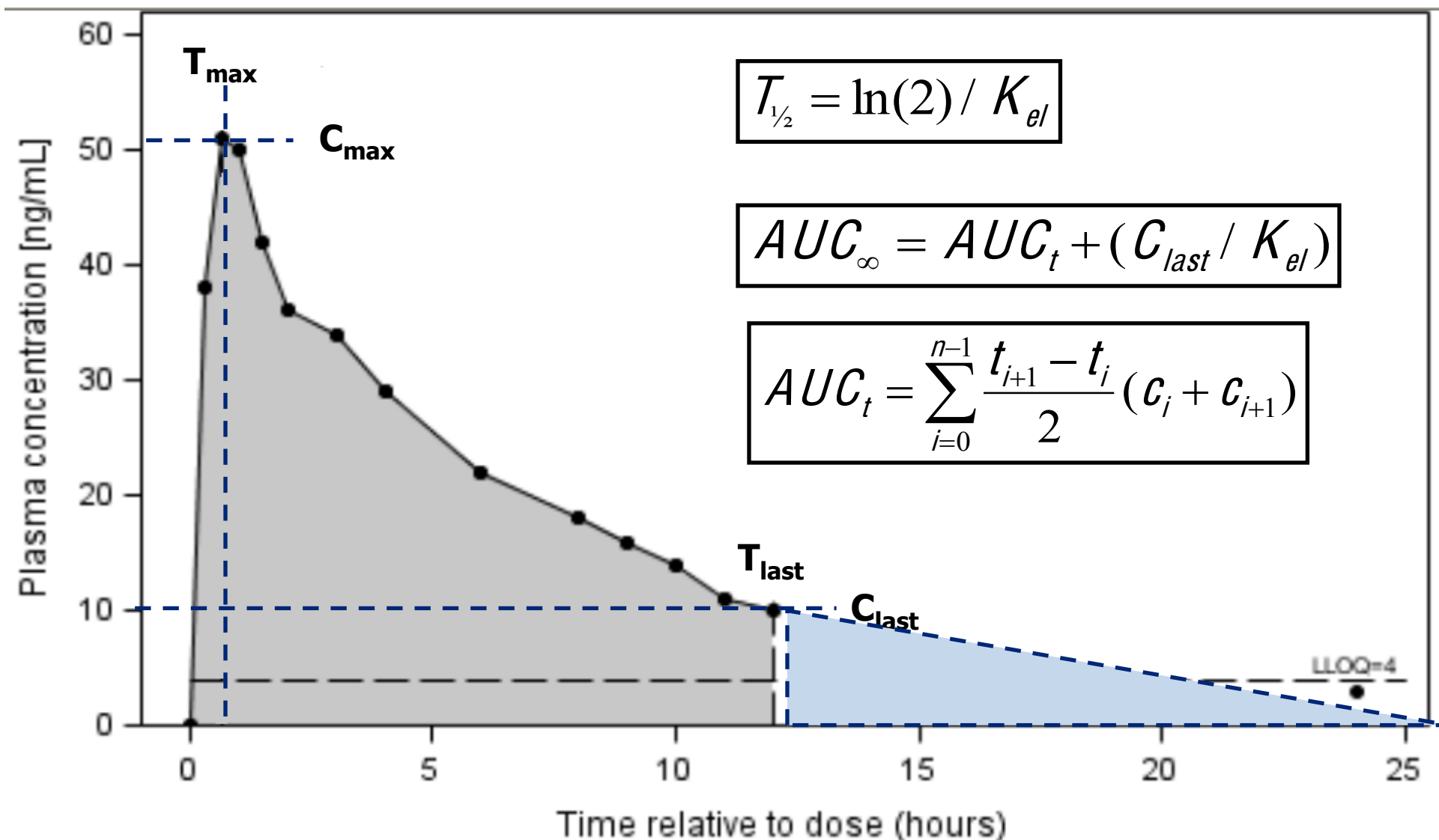
StatFinn Ltd

Calculation details



- The pharmacokinetic parameters are calculated based on non-compartmental analysis.
- The following parameters are calculated directly from concentration data
 - Maximum concentration in the plasma ($C_{\max}$) as the highest plasma concentration value,
 - The time when $C_{\max}$ is reached ($T_{\max}$),
 - The last observed concentration above limit of quantification (C_{last}) and
 - the time when C_{last} is reached (T_{last}).
- The area under the plasma concentration curve (AUC_t) is calculated using the linear trapezoidal rule.

Calculation details



K_{el} estimation



- The elimination rate constant (K_{el})
 - describes the rate of decrease in concentration per time.
 - is estimated from the log-linear terminal part of the concentration-time curve, as the slope of natural logarithm of concentration against time.
 - Data points that belong to the terminal log-linear phase are evaluated based on coefficient of determination, which is calculated with Huber's M robust regression.
 - For each patient the highest coefficient is selected and the corresponding regression model is used in the estimation of K_{el} .

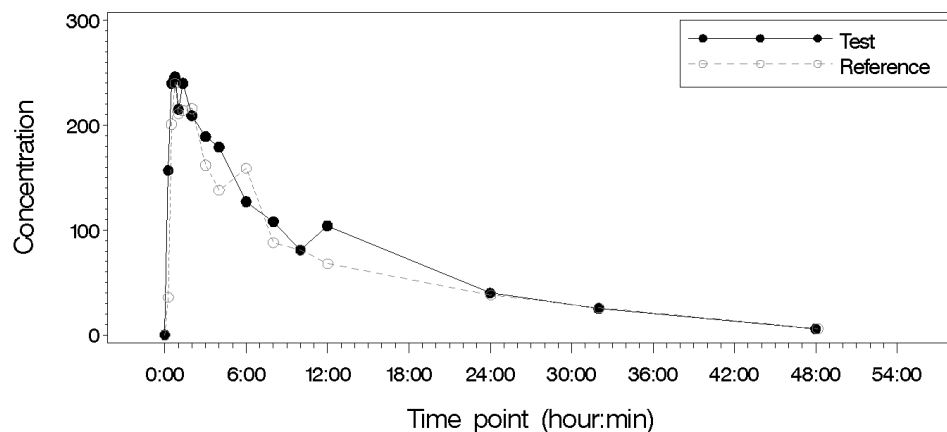
$$Y = \beta_0 + \beta_1 X + \varepsilon$$

```
PROC ROBUSTREG DATA=pc METHOD=M(CONVERGENCE=COEF(EPS=0.0001) MAXITER=999999);  
MODEL log_conc = elapsed;  
RUN;
```

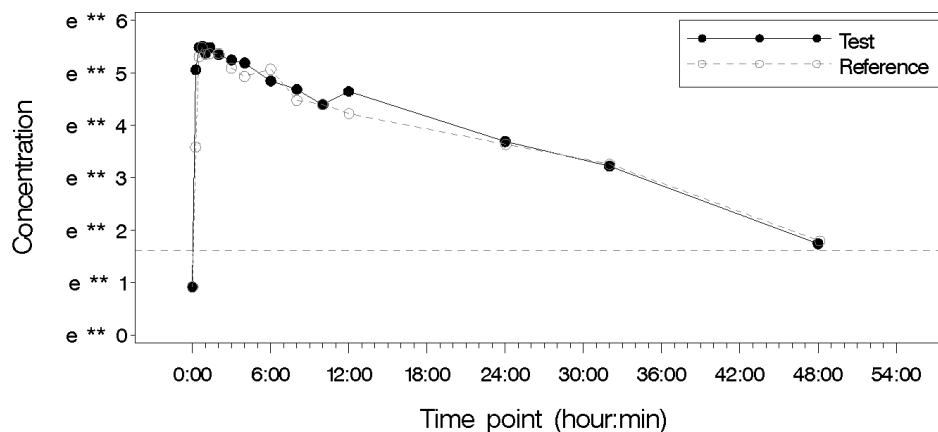
K_{el} estimation



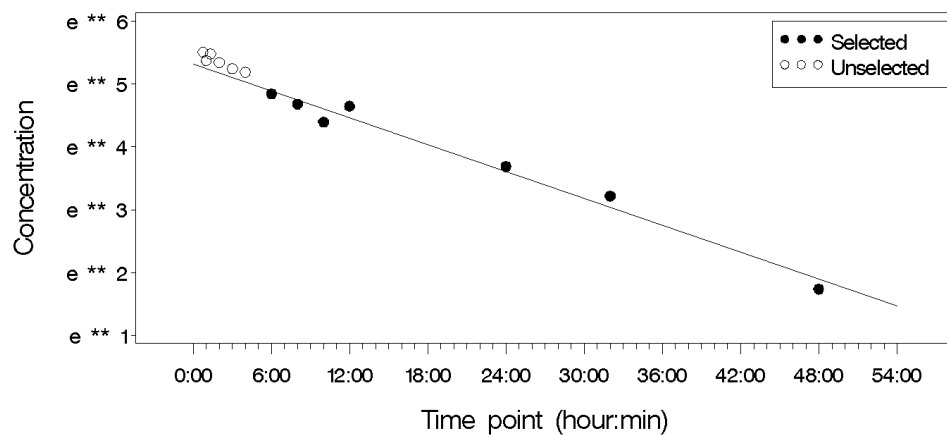
Concentration curve by Formulation



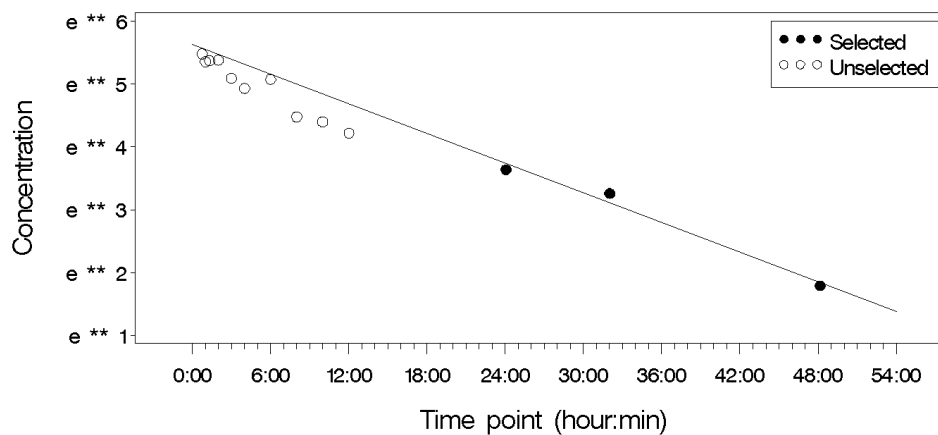
Concentration curve by Formulation (log-scale)



Concentration curve with regression line (Tmax-Tlast) for Test



Concentration curve with regression line (Tmax-Tlast) for Reference



Calculation details



$$T_{1/2} = \ln(2) / K_{el}$$

$$AUC_{\infty} = AUC_t + (C_{last} / K_{el})$$

Formulation	Number of points	Selected	R square	Time range	Cmax	Tmax	AUCt	Kel	AUCinf	Thalf	AUCextrap
Test	3	No	0.9177	23.98	246	0.75	2903.6583	0.0828	2972.4795	8.37	2.3
	4	No	0.7160	36.00	246	0.75	2903.6583	0.0807	2974.2495	8.58	2.4
	5	No	0.8604	37.98	246	0.75	2903.6583	0.0736	2981.1388	9.42	2.6
	6	No	0.9173	39.98	246	0.75	2903.6583	0.0718	2983.0989	9.66	2.7
	7	Yes	0.9242	41.98	246	0.75	2903.6583	0.0712	2983.7548	9.74	2.7
	8	No	0.8915	43.98	246	0.75	2903.6583	0.0726	2982.1189	9.54	2.6
	9	No	0.8823	44.98	246	0.75	2903.6583	0.0735	2981.2259	9.43	2.6
	10	No	0.8818	45.98	246	0.75	2903.6583	0.0742	2980.4668	9.34	2.6
	11	No	0.8558	46.65	246	0.75	2903.6583	0.0752	2979.4164	9.21	2.5
	12	No	0.8486	46.98	246	0.75	2903.6583	0.0753	2979.3339	9.20	2.5
	13	No	0.8459	47.23	246	0.75	2903.6583	0.0759	2978.7549	9.13	2.5

$$AUC_{extrap} = 100 \times [(C_{last} / K_{el}) / AUC_{\infty}]$$

Analysis of variance model

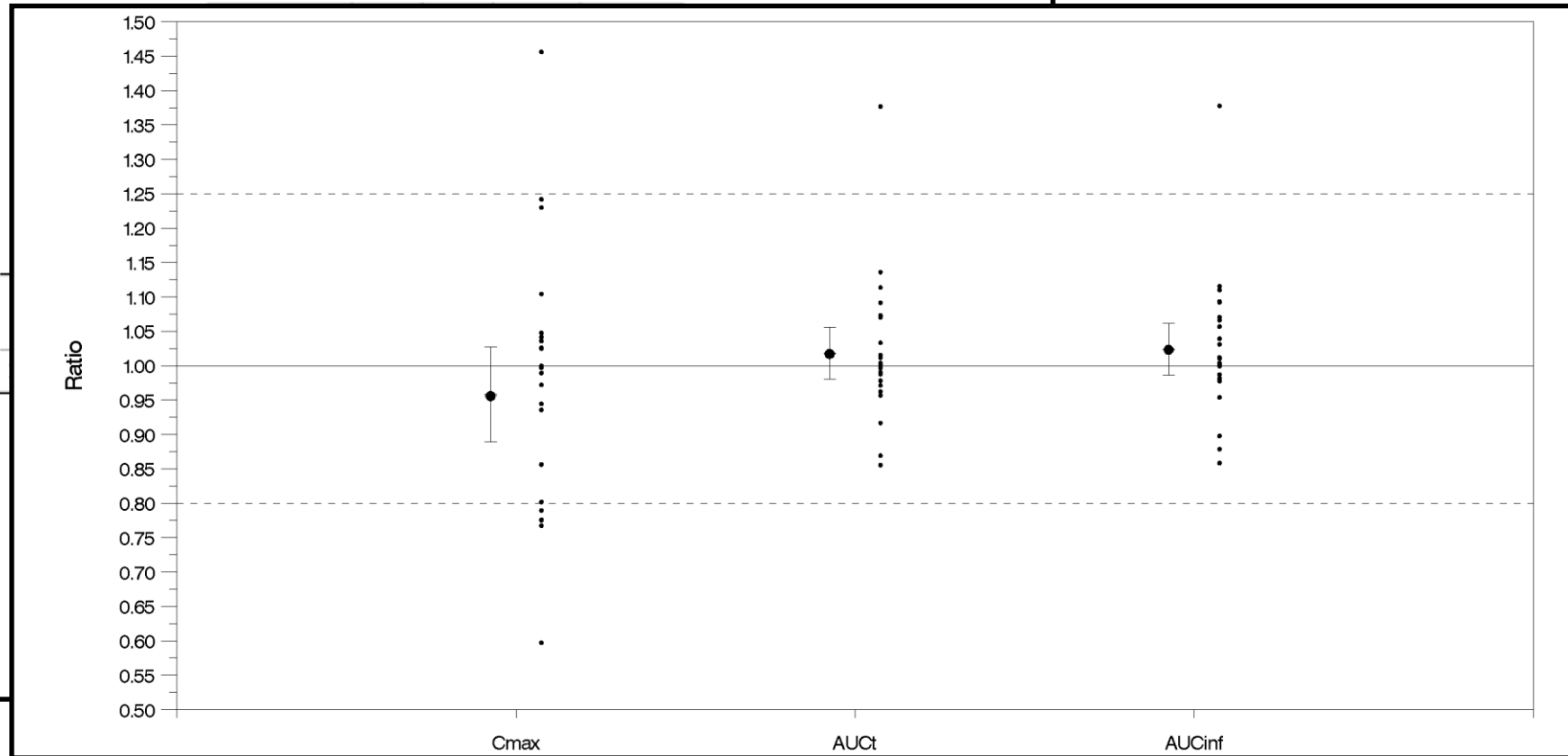
- The assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the population geometric means for the pharmacokinetic parameter.
- A confidence interval for the difference on the log scale between formulations is obtained from analysis of variance model and then back-transformed to obtain the desired confidence interval for the ratio on the original scale.

$$Y_{ijk} = \mu + \xi_{ik} + \pi_j + \tau_{jk} + \gamma_k + \varepsilon_{ijk}$$

```
PROC MIXED DATA=pp ORDER=internal;  
  CLASS usubjid armed visitnum etcd;  
  MODEL log_var=armed visitnum etcd;  
  RANDOM usubjid(armed);  
  ESTIMATE 'Test / Reference' etcd -1 1 / ALPHA=0.1 CL;  
  LSMEANS etcd / ALPHA=0.1 CL;  
RUN;
```

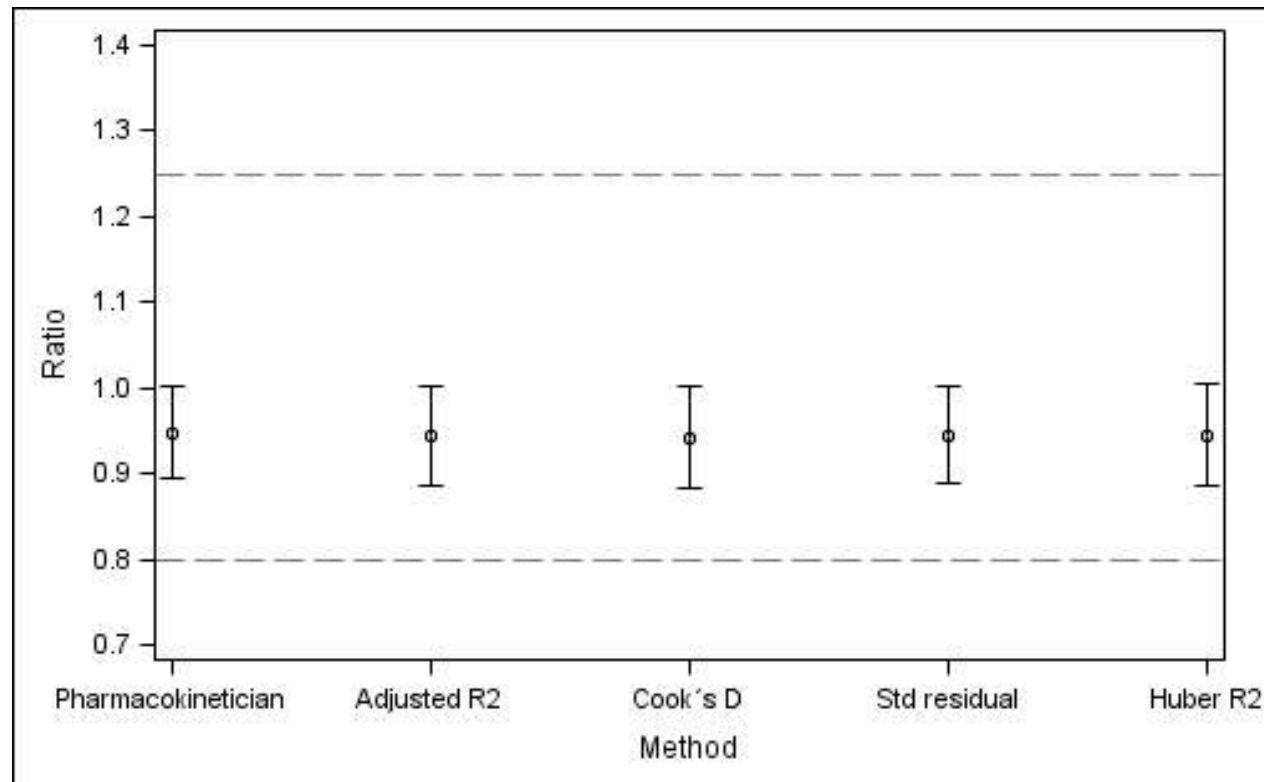
Table 14.2-2.1-3 Summary statistics and statistical analysis of AUCt (hr*g/l) for Metabolite (Page 2 of 2)

Effect	NDF	DDF	F-test	p-value
Treatment	1	20	1.394	0.2515
Sequence	1	20	0.285	0.5994
Period	1	20	0.004	0.9527



Comparison of methods

Ratio of AUC_{∞} with different K_{el} evaluation methods



The bioequivalence conclusion based on AUC_{∞} is the same for any of the methods presented above

Pharmacokinetic Analysis Report



After statistical analyses and other reporting:

1. Pharmacokinetic Analysis report is created based on user defined meta-data which can include:
 - Sponsor, active ingredient of the drug, length of wash-out period, study phase, etc.

STUDY META-DATA AND PARAMETERS		
Name	Description	Value
*SPONSOR	Name of the Sponsor	Firma
*PHASE	Phase of the Study	Phase I
*ACTIVEINGR	Active Ingredient	Activix
*TESTPRODUCT	Test Product Name	Test
*TESTSTRENGTH	Dose of the Test Product	100mg
*TESTFORMULATION	Tested Formulation	Tablet
*REFPRODUCT	Reference Product Name	Origin

2. Individual reports (tables, figures, listings) are combined into the Appendices of Pharmacokinetic Analysis Report.

Pharmacokinetic Analysis Report



SAS code for Pharmacokinetic Analysis Report

```
/******  
%PUT NOTE (&sysmacroname.): Study type and design ;  
/******  
ods rtf text="{\par \tc \b 2 Study type and design \tcl1}";  
  
ods rtf text="MS={outputwidth=100% just=c} MR/RTF'\qj\par' This &PHASE. study was a randomized,  
          &BLINDSTATUS., two-period, single-dose cross-over trial with at least &WASHOUTLENGTH.  
          wash-out period between the treatment periods.";  
  
ods rtf text="MS={outputwidth=100% just=c} MR/RTF'\qj\par' The test and reference products were as follows:";  
  
data tmp;  
length a $10. b $200.;  
do; a="Test"; b="&TESTPRODUCT. &TESTSTRENGTH. &TESTFORMULATION. by &SPONSOR."; output; end;  
do; a="Reference"; b="&REFPRODUCT. &REFSTRENGTH. &REFFORMULATION. by &REFSPONSOR."; output; end;  
label a="Product"  
      b="Description";  
run;  
  
proc print data=tmp noobs label;  
run;
```

Pharmacokinetic Analysis Report



Corresponding section in the final Pharmacokinetic Analysis Report

2 Study type and design

This Phase I study was a randomized, double-blinded, two-period, single-dose cross-over trial with at least 14 days wash-out period between the treatment periods.

The test and reference products were as follows:

□

Product	Description
Test	Activix 100 mg tablet by Firma
Reference	Origin 100 mg tablet by Major Pharmaceuticals

Pharmacokinetic Analysis Report



Finally 3 documents created from the eBEST system

Pharmacokinetic Analysis Report

Pharmacokinetic Analysis Report - Appendix 1

Pharmacokinetic Analysis Report - Appendix 2

Section 16.2 - Patient Data Listings

Study: **ABC123**

Sponsor: **Firma**

Confidential

Pharmacokinetic Analysis Report



Contents of the Appendices of the Pharmacokinetic Analysis Report

Graphics

- Estimated geometric mean ratios
- Mean concentration-time profiles
- Overlaying individual concentration-time profiles
- Individual concentration-time profiles

Tables

- Descriptive statistics of demography
- Summary statistics of PK parameters
- Statistical analysis for PK parameters
- Summary statistics of concentrations
- Summary statistics of sampling times

Listings

- Demographical variables
- Individual subject ratios (Test/Reference)
- Listing of individual PK parameters
- Individual concentration data
- Adverse events

PK calculations

- Individual subject concentration graphs (semi-log)
- Individual subject concentration graphs ($T_{\max}$ - T_{last})
- Line plot (All possibilities)
- Summary of exclusions
- Summary table with all possibilities (points, K_{el} , $\text{AUC}_t/\text{AUC}_{\text{inf}}$, ...)



All this reporting

from concentration data to

Pharmacokinetic Analysis Report and

Appendices

in less that 1 hour