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in a two-fold cross-over design

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Non-blinded randomized phase-I trial in a two-fold cross-over design to assess bioequivalence and residual availability of soya isoflavones of different galenics in pre- and post-menopausal women

Biometrical Report

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Abbreviations

ANOVA:	analysis of variance
BMI:	body mass index
C:	capsule
CV:	coefficient of variation
snr:	screening number
STD:	standard deviation
T:	tablet

List of Parameters and Definitions

Parameter	Definition
$c\_max_{0 \rightarrow 24}$	investigation of bioequivalence: maximum observed concentration within the interval 0 to 24 hours after unique administration of the formulation [nMol/l]
$t\_max_{0 \rightarrow 24}$	investigation of bioequivalence: sampling time at which $c\_max_{0 \rightarrow 24}$ occurred within the interval 0 to 24 hours after unique administration of the formulation [h]
$AUC_{0 \rightarrow 24}$	investigation of bioequivalence: area under the raw concentration versus time curve over the interval 0 to 24 hours [nMol/l*day]
c_max_{res}	investigation of residual availability in period II, day 1 to 28: maximum observed concentration in period II [nMol/l]
t_max_{res}	investigation of residual availability in period II, day 1 to 28: sampling time at which the maximal residual concentration c_max_{res} occurred [d]
AUC_{res}	investigation of residual availability in period II, day 1 to 28: area under the raw residual concentration versus time curve over the interval 1 to 28 days [nMol/l*day]

1 Table of content

2 Design and Plan of the Study

In gynaecology, there was an increasing importance of an investigation of alternative therapeutic options over the last years because of possible risks of hormone replacement therapy. Phyto-estrogenes like soya isoflavones became more and more important in the treatment of women with menopausal complaints. The metabolism of soya isoflavones is poorly understood at present. Several studies were carried out to better understanding of the process (SETCHELL [2002]).

This study was performed to investigate the bioequivalence and the residual availability of soya isoflavones given in the two formulations capsule and tablet. The study participants were pre- and post-menopausal women. The first main goal of the study was to compare the bioequivalence of genistein, daidzein, equol, and the total sum of isoflavones after unique administration of the drug. The second main goal was to assess the residual availability of genistein, daidzein, equol, and the total sum of isoflavones after daily administration of the drug over a period of 28 days. The study endpoints were the concentrations of genistein, daidzein, and equol measured at several points (see Figure 1). The statistical analyses focuses on the pharmacokinetic parameters AUC, c_{max} and t_{max} taken for every isoflavone and for the sum of all isoflavones. An additional intention was to evaluate potential complaints during participation of the study.

2.1 Participants

The study was planned for healthy women aged from 45 to 60 years, who had a body mass index (BMI) between 20 and 30 kg/m^2. The participation was excluded if one or more of the following criteria met:

- administration of antibiotics over the last 6 months,
- administration of additional supplements (vitamin C, vitamin D3, vitamin E, folic acid, zinc, and iron),
- serious diseases of the metabolism, abuse of alcohol or drugs, serious gastro-intestinal diseases with resorptional dysfunction, use of abstergent agents, malignant tumors except skin cancer.

The ethical approval was obtained by the ethics committee of the University of Heidelberg before the recruitment began. The informed consent was obtained from each participant after explanation of the nature and possible consequences of the study.

2.2 Trial Design and Randomization

The study was designed as a non-blinded, two-fold cross-over design with two treatment periods (treatment periods I and II) and randomized allocation of the subjects to one of the two sequences of formulation:

- sequence 1: administration of a capsule in period I and afterwards a tablet in period II
- sequence 2: administration of a tablet in period I and afterwards a capsule in period II.

The tablet is characterized by a retarded availability of isoflavones. The capsule is characterized by a fast availability of the isoflavones. Both, capsule and tablet contain a concentration of 80 mg isoflavone (genistein and daidzein) from soya extract, additionally vitamins, iron, zinc, and lecithin.

Figure 1 shows the flow chart of the study.

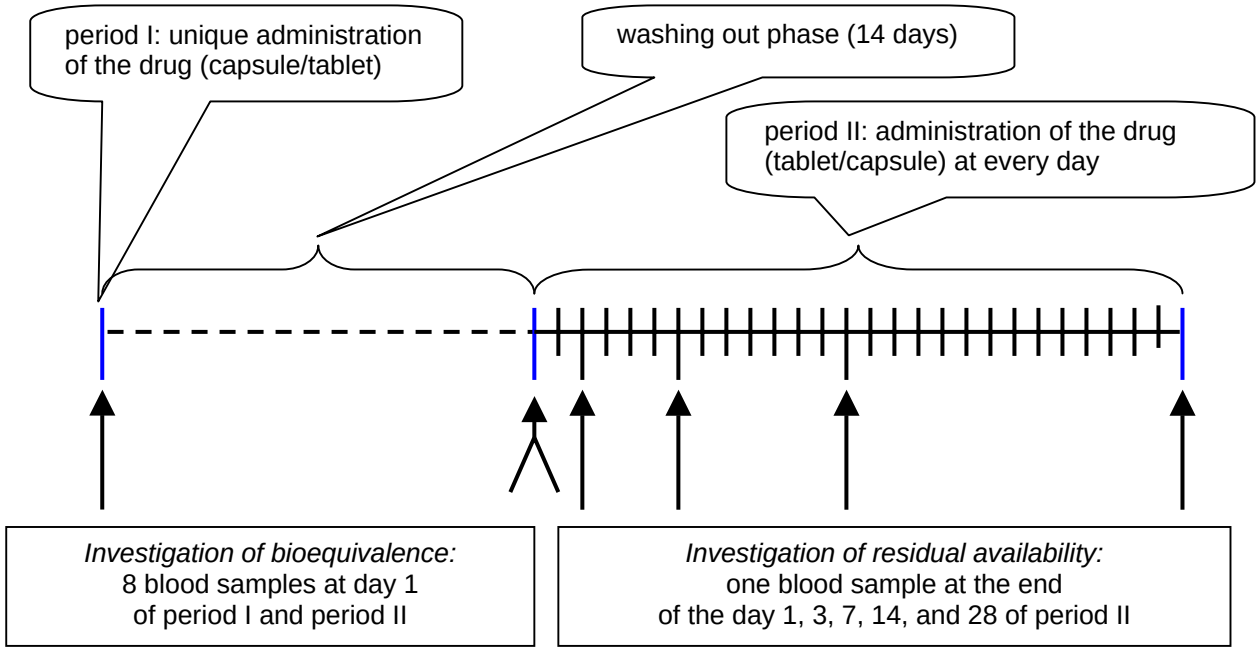

Figure 1: Flow chart of the study.

The study starts with **period I**, with an unique administration of the drug (capsule in sequence 1 and tablet in sequence 2). The total length of period I is one day. Blood samples are taken at 8 time points: before and 0.5, 1, 2, 3, 6, 12, and 24 hours after administration of the drug.

The **period II** starts after a washing out phase of 14 days. The total length is 28 days. The administration of the drug is performed at every day (tablet in sequence 1 and capsule in sequence 2). Blood samples are taken at the following time points: before and 0.5, 1, 2, 3, 6, 12, and 24 hours after the administration of the drug at the first day of period II. Additionally, one blood sample at the end of the day 1, 3, 7, 14, and 28 of period II was taken to measure the residual concentration of the isoflavones. These additional blood samples were taken 24 h after drug administration.

The total duration of the trial for each participant is 43 days.

2.3 Primary and secondary endpoints

The primary study endpoints were the concentrations of genistein, daidzein, and equol measured at 8 time points at day 1 in period I and at day 1 in period II. Additionally, the residual concentration of genistein, daidzein, and equol was measured at the end of the days 1, 3, 7, 14, and 28 in period II. An overview shows Figure 1.

To investigate the bioequivalence after unique administration, the following pharmacokinetic parameters were calculated for the isoflavones in period I and in period II:

- maximum observed concentration ($c\_max_{0\rightarrow 24}$ in nMol/l)
- sampling time at which $c\_max_{0\rightarrow 24}$ occurred ($t\_max_{0\rightarrow 24}$ in h)

- area under the raw concentration versus time curve over the interval 0 to 24 hours using the linear trapezoidal rule ($AUC_{0\rightarrow 24}$ in nMol/l*day).

To investigate the residual availability after daily drug administration over 28 days, the following pharmacokinetic parameters were calculated for the isoflavones in period II:

- maximum observed residual concentration (c_max_{res} in nMol/l)
- sampling time at which the maximal residual concentration c_max_{res} occurred (t_max_{res} in day)
- area under the raw residual concentration versus time curve over the interval 1 to 28 days using the linear trapezoidal rule (AUC_{res} in nMol/l*day).

A further intention of the trial was an assessment of potential complaints associated with the administration of soya drugs. Therefore, as a secondary endpoint, the potential complaints were measured by a self-constructed score at the beginning and at the end of the study. The difference in this score was calculated to assess the change in potential complaints. Additionally, at the end of the study the participants were asked whether there is a change in feeling since the start of the study. An example of the questionnaire is included in the appendix.

3 Statistical Analysis

The main statistical analysis of this two-period cross-over bioequivalence study is based on SENN [1993], SAUTER [1992], and CPMP [2001].

The sample size calculation is based on the assumption that the log-transformed pharmacokinetic parameters are normally distributed with a coefficient of variation of 0.15. The range of bioequivalence is assumed with +/- 20%. A significance level of 5% and a power of 80% is reached with a total sample size of 20 participants. All tests were performed at the significance level 0.05. An adjustment for multiple testing was not done. The statistical analysis was performed as per-protocol analysis. For all logarithmic transformations of the data, the natural logarithm *ln* was used.

The decision in favor of bioequivalence was based on the inclusion of the 90% confidence interval. Thus,

- for $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$ the accepted limits of bioequivalence range are 0.80 and 1.25, see page 180 of SENN [1993],
- for $t\_max_{0\rightarrow 24}$ the accepted limits of bioequivalence range are expressed in absolute differences hours, which corresponds to +/- 20% of the expected mean of $t\_max_{0\rightarrow 24}$ of the capsule formulation (SAUTER [1992], STEINIIJANS [1988]).

Both, graphical and analytical methods were used. All measurements and the pharmacokinetic parameters are presented in tabular form. A time-concentration plot is made for daidzein, genistein, equol, and the sum of all isoflavones for every study subject. Additionally, box-plots of the log-transformed values of genistein, daidzein, and sum of all isoflavones are presented for day 1 of period I (8 time points), day 1 of period II (8 time points), and for the 28 days of drug administration in period II (5 time points). Cross-over differences (capsule minus tablet) and period differences (period II minus period I) for the log-transformed

pharmacokinetic parameters $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$ and for the parameter $t\_max_{0\rightarrow 24}$ are presented in tabular form. Additionally, response by periods plots and groups by period plots are made for this parameters.

To assess the influence of period, treatment, and sequence on the parameters of interest, analysis of variance (ANOVA) was performed. For the parameters $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$, ANOVA on the log-transformed data was carried out. For the parameter $t\_max_{0\rightarrow 24}$, ANOVA was performed on the raw data. All analyses were carried out using the procedure *glm* in the SAS software, version 8.2 (proposed at page 63f of SENN [1993], page 270 of LITTEL [2002]). In all ANOVA models, the treatment sequence, the period, and the formulation were included as fixed effect. Additionally, the single participant was included as random effect.

To calculate the difference between the capsule and tablet formulation, ordinary least squares analyses on the log-transformed values of $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$ was performed using the procedure *glm*. For each parameter of interest, the ratio "capsule/tablet" was calculated from the least squares estimators. The standard error of the difference "capsule - tablet" with the 95% percentiles of the respective t-distribution was used to calculate the two-sided 90% confidence intervals for the ratio "capsule/tablet", see page 72f of SENN [1993].

To assess the bioequivalence, a per-protocol analysis was carried out. The ratio "capsule/tablet" was calculated for the log-transformed values of $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$. Bioequivalence was accepted if the 90% confidence intervals for the measures of relative bioavailability were lying within an acceptance interval of 0.80 and 1.25, see page 318f of SENN [1997].

Ideas from SAUTER [1992] and STEINIJANS [1998] were used to compare the bioequivalence of the parameter $t\_max_{0\rightarrow 24}$. The bioequivalence ranges are expressed in absolute differences of ± 20% of the expected value of $t\_max_{0\rightarrow 24}$ for the capsule formulation. Bioequivalence was accepted if the non-parametric 90% confidence intervals for the difference between capsule and tablet were lying within this range (HAUSCHKE [1990], chapter 7 of PEACE [1988]). ANUPONGSANUGOOL [2005] gives an expected value of 6 h for $t\_max_{0\rightarrow 24}$ for the capsule formulation, which is assumed as the same for genistein, daidzein, and total sum of isoflavones. Thus, the respective interval for acceptance of bioequivalence for $t\_max_{0\rightarrow 24}$ is from –1.2 h to 1.2 h.

To assess the residual availability of the isoflavones over 28 days in period II, the parameters of interest were investigated using explorative data analysis. Based on part 9.6 in ALTMAN [1993], the parameters AUC_{res} and c_max_{res} were analysed using parametric 95% confidence intervals for the difference between the means of the log-transformed values of the tablet and the capsule formulation. Additionally, two sample t-tests were performed on the log-transformed values. To analyse the parameter t_max_{res}, the non-parametric 95% confidence intervals for the difference of the medians between the tablet and the capsule formulation were calculated, see chapter 5 of ALTMAN [2000]. Additionally, WILCOXON rank sum tests on the raw data were carried out.

The comparison of the score to evaluate the difference in potential complaints was performed by the WILCOXON signed rank test.

4 Accomplishment of the study

4.1 Responsibilities

The study was carried out at the University Women's Hospital (department of Gynaecological Endocrinology and Fertility Disorders), University of Heidelberg, which was responsible for recruiting of participants, data collection, data management, and data quality. All physical and chemical analyses were carried out at the German Cancer Research Center in Heidelberg. The generation of the randomization list and all statistical analyses were performed at the Department of Medical Biometry and Informatics (IMBI), University of Heidelberg.

4.2 Participants

All participants were randomized between June 2004 and August 2004. Staff members from the University Women's Hospital and her relatives were recruited into the study. In total, 23 voluntary women were randomized. Table 1 shows the treatment periods and the allocation of participants.

Table 1: Treatment periods and allocation of treatments.

Treatment sequences	**Treatment period I**	**Treatment period II**
1 (n = 12 subjects, from 2 subjects only data from period I are available)	capsule	tablet
2 (n = 11 subjects, 1 subject dropped out after randomization, from 1 subject only data from period II are available)	tablet	capsule

One woman has withdrawn from study after randomization (snr 4, randomized to treatment sequence 2). The reason was pain after applying a canula for blood sampling. From one woman (snr 1, randomized to treatment sequence 2) only measurements from period II are available: The measurement of the isoflavones in period I was not possible because of unknown reasons. Two women (snr 16 and snr 23, both randomized to treatment sequence 1) have left the study after finishing the period I. The reason for snr 23 was a circulatory collapse after administration the first tablet in period II. Participant snr 16 was later excluded because of Hashimoto thyreoiditis. In total, the data from period I and period II from 19 subjects were available for the analysis of bioequivalence.

For the analysis of the residual availability, the data from 20 participants were available.

The questionnaire for the assessment of potential complaints associated with the administration of soya drugs was filled by 20 women at the beginning and at the end of the study.

4.3 Randomization of Participants

Table A 1 shows the randomization scheme of the study. Measurements from both periods were available from 10 participants in treatment sequence 1 and from 9 participants in treatment sequence 2, see part 2.2.

Table 2 shows the main characteristics from the study population after randomization for these participants, who contributed the measurements from both periods. The comparisons for both treatment sequences were performed using the WILCOXON rank sum test. The results suggest no differences in the characteristics age height, weight, and body mass index (BMI).

Table 2: Demographic data and comparison of the treatment sequences.

	Capsule/Tablet N=10	**Tablet/Capsule N=9**	**Total N=19**	**p-value**
Age [years]				
- N	10	9	19	0.304
- Mean +/- SD	51.8 +/-5.3	53.7 +/-3.4	52.7 +/-4.5	
- p5, p25, p75, p95	46.0, 47.0, 54.0, 63.0	50.0, 51.0, 56.0, 59.0	46.0, 50.0, 55.0, 63.0	
- Median	52.5	52.0	52.0	
- Min, Max	46.0, 63.0	50.0, 59.0	46.0, 63.0	
Height [m]				
- N	10	9	19	0.386
- Mean +/- SD	1.7 +/-0.1	1.6 +/-0.1	1.6 +/-0.1	
- p5, p25, p75, p95	1.5, 1.6, 1.7, 1.8	1.5, 1.5, 1.7, 1.7	1.5, 1.6, 1.7, 1.8	
- Median	1.7	1.7	1.7	
- Min, Max	1.5, 1.8	1.5, 1.7	1.5, 1.8	
Weight [kg]				
- N	10	9	19	0.220
- Mean +/- SD	67.6 +/-12.6	61.1 +/-3.5	64.5 +/-9.8	
- p5, p25, p75, p95	48.0, 59.0, 76.0, 89.5	57.5, 58.0, 62.0, 68.0	48.0, 58.0, 68.0, 89.5	
- Median	63.3	61.0	62.0	
- Min, Max	48.0, 89.5	57.5, 68.0	48.0, 89.5	
Body mass index				
- N	10	9	19	0.775
- Mean +/- SD	24.7 +/-4.7	23.5 +/-1.6	24.1 +/-3.5	
- p5, p25, p75, p95	17.6, 21.5, 28.0, 32.9	20.8, 22.4, 24.9, 25.1	17.6, 22.0, 25.1, 32.9	
- Median	23.6	23.8	23.8	
- Min, Max	17.6, 32.9	20.8, 25.1	17.6, 32.9	

4.4 Analysis of Primary and Secondary endpoints

To compare the $AUC_{0\rightarrow 24}$ for different participants, the concentrations of isoflavones for the time points “0 h” and “24 h” at day 1 in period I and at day 1 in period II were interpolated using straight lines. If the maximum observed concentration was measured before “0 h” resp. after “24 h”, the pharmacokinetic parameter $t\_max_{0\rightarrow 24}$ was set to “0 h” resp. to “24 h” and for the pharmacokinetic parameter $c\_max_{0\rightarrow 24}$ the interpolated value at the time point “0 h” resp. “24 h” was used.

To compare the AUC_{res} for different participants, the concentrations of isoflavones for “day 28” in period II were interpolated using straight lines. If the maximum observed residual concentration in period II was measured after “day 28”, the pharmacokinetic parameter t_max_{res} was set to “day 28” and for the pharmacokinetic parameter c_max_{res} the interpolated value for “day 28” was used. For day 1 of period II, no interpolation was necessary because the measurements were taken at the end of day 1 for all participants.

5 Results

5.1 Descriptive Analysis and Graphical Data Exploration

The measurements of the isoflavones are presented in sixteen tables in the appendix. Table A 2, Table A 3, Table A 4, and Table A 5 show the concentration of daidzein, genistein, equol, and the total sum of isoflavones for the tablet formulation. Table A 6, Table A 7, Table A 8, and Table A 9 show the concentration of daidzein, genistein, equol, and the total sum of isoflavones for the capsule formulation. Table A 10, Table A 11, Table A 12, and Table A 13 show the residual concentrations for the tablet formulation, Table A 14, Table A 15 , Table A 16, and Table A 17 show the residual concentration for the capsule formulation.

The pharmacokinetic parameters to investigate bioequivalence are presented in the following six tables in the appendix. Table A 18, Table A 19, and Table A 20 show the parameters $AUC_{0\rightarrow 24}$, $c\_max_{0\rightarrow 24}$, $t\_max_{0\rightarrow 24}$ for daidzein, genistein, and the total sum of isoflavones for the tablet formulation. Table A 21, Table A 22, and Table A 23 show the parameters $AUC_{0\rightarrow 24}$, $c\_max_{0\rightarrow 24}$, $t\_max_{0\rightarrow 24}$ for daidzein, genistein, and the total sum of isoflavones for the capsule formulation. There are no tables for equol because there was no participant, who produced equol in period I and at day 1 of period II.

The pharmacokinetic parameters to compare the residual availability after daily drug administration over 28 days in period II are presented in the following tables. Table A 24, Table A 25, Table A 26, and Table A 27 show the pharmacokinetic parameters AUC_{res}, c_max_{res}, t_max_{res} for daidzein, genistein, equol, and the total sum of isoflavones for all subjects given the tablet formulation in period II. Table A 28, Table A 29, Table A 30, and Table A 31 show the pharmacokinetic parameters AUC_{res}, c_max_{res}, t_max_{res} for daidzein, genistein, equol, and the total sum of isoflavones for all participants given the capsule formulation in period II.

Figure A 1 shows the plot of the concentration-time profiles for daidzein, genistein, and sum of all isoflavones in period I and at day 1 in period II for every study subject. The formulation (capsule or tablet) was uniquely administered at the beginning of each period.

Figure A 2 shows the plot of the concentration-time profiles for residual concentration of daidzein, genistein, equol, and sum of all isoflavones at the days 1, 3, 7, 14, and 28 of period II for every study subject. There are plots for equol only for snr 6 and snr 7. Box-plots of the log-transformed values of daidzein, genistein, and sum of all isoflavones for the capsule- and tablet formulation in period I, day 1 of period II, and for the days 1, 3, 7, 14, and 28 of period II show Figure A 3, Figure A 4, and Figure A 5. Response-by-period plots for the log-transformed values of $AUC_{0\rightarrow 24}$, $c\_max_{0\rightarrow 24}$, and for $t\_max_{0\rightarrow 24}$ for daidzein, genistein, and the sum of all isoflavones are presented in Figure A 6. Groups-by-periods plots for the log-transformed values of $AUC_{0\rightarrow 24}$, $c\_max_{0\rightarrow 24}$, and for $t\_max_{0\rightarrow 24}$ for daidzein, genistein and sum of all isoflavones for both treatment sequences are shown in Figure A 7.

5.2 ANOVA

The ANOVA results for the per-protocol analysis of bioequivalence for the parameters of interest are given

- for daidzein in Table A 32, Table A 33, and Table A 34

- for genistein in Table A 35, Table A 36, and Table A 37
- for the sum of all isoflavones in Table A 38, Table A 39, and Table A 40.

The correct p-values for the sequence effects were obtained using the "test" option in the SAS procedure *glm*.

The following Table 3 summarizes these p-values, which gives an indication of the presence of carry over.

Table 3: Sequence effects in the ANOVA models.

parameter	ln($AUC_{0\rightarrow 24}$)	ln(c_$max_{0\rightarrow 24}$)	t_$max_{0\rightarrow 24}$
daidzein	0.028	0.002	0.216
genistein	0.467	0.155	0.042
sum of all isoflavones	0.330	0.058	0.055

At the level 5%, there are an indication for non ignorable sequence effects for the parameters ln($AUC_{0\rightarrow 24}$) and ln(c_$max_{0\rightarrow 24}$) for daidzein, and for the parameter t_$max_{0\rightarrow 24}$ for genistein. This indicates that in spite of the long washing out phase of 14 days, carry over effects may play a role. To assess the bioequivalence in the following part 5.3, the sequence was included as fixed effect in all ANOVA models. Hence, a possible carry over effect is considered in calculating the ratios "capsule/tablet" and the respective confidence intervals. Additionally, a comparison of the pharmacokinetic parameters of interest only for period I was performed, see part 5.3.

Table 4: Period effects in the ANOVA models.

	ln($AUC_{0\rightarrow 24}$)	ln(c_$max_{0\rightarrow 24}$)	t_$max_{0\rightarrow 24}$
daidzein	0.013	0.071	0.991
genistein	0.057	0.080	0.950
sum of all isoflavones	0.037	0.065	0.732

Table 4 shows the p-values for the period effects of the ANOVA analysis. At the 5% level, the results indicate a period effect for the log-transformed value of $AUC_{0\rightarrow 24}$ of daidzein and sum of all isoflavones. An adjusting for the period effects was not done. However, in the analysis of bioequivalence (part 5.3), the period was included as fixed effect in all ANOVA models. Hence, the effect of the period is considered in the calculation of the ratios "capsule/tablet" and the respective confidence limits.

Table 5: Treatment effects in the ANOVA models.

parameter	ln($AUC_{0\rightarrow 24}$)	ln(c_$max_{0\rightarrow 24}$)	t_$max_{0\rightarrow 24}$
daidzein	0.034	0.001	0.002
genistein	0.008	0.004	0.064
sum of all isoflavones	0.012	0.003	0.007

Table 5 summarizes the p-values related to the treatment effect. At the 5% level, the results presented in Table 5 indicate a remarkable effect for all parameters of interest, with exception of t_$max_{0\rightarrow 24}$ for genistein.

5.3 Analysis of Bioequivalence and Residual Availability

Bioequivalence of the parameters $AUC_{0\rightarrow 24}$, $c\_max_{0\rightarrow 24}$, $t\_max_{0\rightarrow 24}$

To assess the bioequivalence, the period sums, the period differences, and the cross-over differences for the log-transformed values of $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$ and for the parameter $t\_max_{0\rightarrow 24}$ were calculated. Table A 41, Table A 42, and Table A 43 show this pharmacokinetic parameters for daidzein. Table A 44, Table A 45, and Table A 46 show the parameters for genistein. Table A 47, Table A 48, and Table A 49 show the parameters for the sum of all isoflavones. The statistical method for assessing the relative bioavailability is based upon the 90% confidence intervals for the ratio "capsule/tablet" for the log-transformed values of $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$. The calculations are based on the differences in the least-squares means, which were used because of the unequal number of subjects per sequence (chapter 5.2.3 of LITTELL [2002]).

For the log-transformed values of $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$, the ratio "capsule/tablet" was calculated using the difference in the least-squares means estimation for each formulation. The confidence limits were obtained using the standard error of the difference in the least-squares means and the 95%-percentile of the respective t-distribution. All analyses were performed as per-protocol. The results of the bioequivalence data are given in Table 6 and Table 7.

Table 6: Bioequivalence intervals for the log-transformed values of $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$ for daidzein, genistein, and sum of all isoflavones.

parameter	lower bound estimation	ratio "capsule/tablet"	upper bound estimation
daidzein: $\ln(AUC_{0\rightarrow 24})$	1.139	1.692	2.515
daidzein: $\ln(c\_max_{0\rightarrow 24})$	1.766	2.667	4.028
genistein: $\ln(AUC_{0\rightarrow 24})$	1.334	1.997	2.990
genistein: $\ln(c\_max_{0\rightarrow 24})$	1.495	2.309	3.568
sum of all isoflavones: $\ln(AUC_{0\rightarrow 24})$	1.280	1.907	2.840
sum of all isoflavones: $\ln(c\_max_{0\rightarrow 24})$	1.519	2.274	3.405

The results show that for none of the parameters the bioequivalence passes. For every parameter (except $\ln(AUC_{0\rightarrow 24})$ for daidzein), the 90% confidence interval is not included in the acceptance interval of 0.80 and 1.25. For daidzein the log-transformed value of $AUC_{0\rightarrow 24}$ is partly included in the acceptance interval. Hence, a decision about bioequivalence is not possible.

To assess the bioequivalence for the parameter $t\_max_{0\rightarrow 24}$, the *Hodges–Lehmann estimators* and the 90% confidence limits for the difference between capsule and tablet were calculated (page 85ff of SENN [1993]). The results for the per-protocol analysis are shown in Table 7. The critical value was obtained from Table H in BORTZ [2003].

Table 7: *Hodges-Lehmann estimators* and the 90% confidence limits for the difference "capsule-tablet" of the parameter $t\_max_{0\rightarrow 24}$ for daidzein, genistein, and sum of all isoflavones.

parameter	lower bound estimation	difference	upper bound estimation
daidzein: $t\_max_{0\rightarrow 24}$	-6.225	-4.233	-2.540
genistein: $t\_max_{0\rightarrow 24}$	-6.075	-3.575	-1.710
sum of all isoflavones: $t\_max_{0\rightarrow 24}$	-5.640	-3.888	-1.990

The results in Table 7 show that for daidzein, genistein, and sum of all isoflavones for the parameter $t\_max_{0\rightarrow 24}$ no bioequivalence passes: The bounds of the 90% confidence intervals are not included in the respective ranges of bioequivalence (from –1.2 h to 1.2 h), see part 3. The calculated values for the parameter $t\_max_{0\rightarrow 24}$ for daidzein, genistein, and total sum of isoflavones (capsule formulation: 2.55, 2.51, and 3.01, see Table A 21, Table A 22, and Table A 23; tablet formulation: 6.08, 6.07, and 6.07 see Table A 18, Table A 19, and

Table A 20) are much lower than the expected value of 6 h for the capsule formulation and 12 h for the tablet formulation. A smaller expected value of $t\_max_{0\rightarrow 24}$ for the capsule formulation (e.g. 2.5 h) would lead to a smaller range for acceptance of bioequivalence (e.g. from –0.5 h to 0.5 h). In this case, also no bioequivalence would pass.

Because of possible carry over effects (see Table 3 in part 5.2), an additional comparison of the pharmacokinetic parameters only for period I was performed. For the log-transformed values of $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$, the ratio "capsule/tablet" was calculated using the difference in the means for each formulation given in period I. The results of the bioequivalence data shows Table A 50. The confidence limits were obtained using the standard error of the difference in the means and the 95%-percentile of the respective t-distribution. For every parameter of interest, the 90% confidence interval is partly included in the acceptance interval. Thus, a decision about bioequivalence is not possible either. To assess the bioequivalence for the parameter $t\_max_{0\rightarrow 24}$, for daidzein, genistein, and total sum of isoflavones the median differences between the capsule and tablet formulation were calculated. The calculation of the non-parametric 90% confidence limits for the differences in the median between capsule and tablet is based on chapter 5 of ALTMAN [2000]). The results are shown in Table A 51. The critical value was obtained from Table 18.5 in ALTMANN [2000]. The bounds of the 90% confidence intervals are not included in the respective ranges of bioequivalence (from –1.2 h to 1.2 h), see part 3. Thus, a decision about bioequivalence is not possible either.

Residual availability: analysis of the parameters AUC_{res}, c_max_{res}, t_max_{res}

To compare the residual availability between capsule and tablet, for the parameters AUC_{res} and c_max_{res} for daidzein, genistein, and sum of all isoflavones the parametric 95% confidence intervals for the difference between the means of the log-transformed values of the tablet and the capsule formulation were calculated. The analysis is based on chapter 9.6 of ALTMAN [1993]. Additionally, two-sample t-tests were performed on the log-transformed values.

To analyse the parameter t_max_{res}, the non-parametric 95% confidence intervals for the difference of the medians of the tablet and the capsule formulation were calculated, based on chapter 5 of ALTMAN [2000]. Additionally, WILCOXON rank sum tests on the raw data were carried out.

For the difference between the means of the log-transformed values of AUC_{res} and c_max_{res}, the mean difference between the tablet and the capsule formulation and the parametric 95% confidence intervals are summarized in Table 8. Additionally, the results of the t-tests are presented in this table.

For the parameter t_max_{res}, the median difference between the tablet and the capsule formulation and the non-parametric 95% confidence intervals for the difference between the medians are summarized in Table 9. Additionally, the results of the WILCOXON rank sum tests are presented in this table.

In total, the data from 20 participants were available for the investigation of the residual availability. In contrast to the investigations of bioequivalence, the sum of all isoflavones in the investigations of residual variability includes the equol, which only was produced by snr 6 and snr 7.

Table 8: Residual availability: analysis of the log-transformed values of AUC_{res} and c_max_{res} for tablet and capsule: differences between the mean, parametric 95% confidence intervals for the differences and results of the two sample t-tests.

parameter	**difference in the means 'tablet-capsule' [95% confidence interval for the difference]**	**p-value**
daidzein: $\ln(AUC_{res})$	0.836 [-0.366 – 2.039]	0.161
daidzein: $\ln(c\_max_{res})$	0.648 [-0.690 –1.987]	0.321
genistein: $\ln(AUC_{res})$	0.237 [-0.284 – 0.758]	0.351
genistein: $\ln(c\_max_{res})$	0.143 [-0.509 – 0.795]	0.650
sum of all isoflavones: $\ln(AUC_{res})$	0.298 [-0.249 – 0.845]	0.267
sum of all isoflavones: $\ln(c\_max_{res})$	0.202 [-0.504 – 0.907]	0.556

Table 9: Residual availability: analysis of t_max_{res} for tablet and capsule: differences between the medians, non-parametric 95% confidence intervals and results of the WILCOXON rank sum tests.

parameter	**difference in the medians 'tablet-capsule' [95% confidence interval for the difference]**	**p-value**
daidzein: t_max_{res}	0.0 [-14.0 – 11.0]	0.876
genistein: t_max_{res}	0.0 [-5.0 – 14.0]	0.588
sum of all isoflavones: t_max_{res}	7.0 [-4.0 – 21.0]	0.277

The results in Table 8 and Table 9 show no significant difference in the parameters of interest between the capsule and the tablet formulation because of the large confidence intervals.

5.4 Assessment of potential complaints

To assess potential complaints associated with the administration of soya drugs, a questionnaire was filled in at the beginning and at the end of the study. In total, the data from 20 participants were available.

Six subscales were used to measure potential complaints: general wellbeing, cardiovascular system, digestive system and frequency of defecation (per day), musculoskeletal system, uro-genital system. The sum of these subscales was used to measure the general wellbeing. Additionally, at the end of the study the participants

were asked whether there is a change in feeling since the start of the study. An example of the questionnaire is included in the appendix.

The difference in the total scale and in all subscales was calculated to measure the change in potential complaints. All comparisons were performed by the WILCOXON signed rank test. The medians and respective inter quartile ranges of the subscales and the results of the WILCOXON signed rank tests for all participants are summarized in Table 10.

Table 10: Median and inter quartile ranges of the subscales at the beginning and at the end of the study, for the difference, and results from the WILCOXON signed rank tests for all participants.

scale	begin of study (median (IQR*))	end of study (median (IQR*))	difference in the score (median (IQR*))	p-value
general wellbeing	10.0 (5.5 – 17.5)	5.5 (2.0 – 14.5)	-2.0 (-4.5 – 1.0)	0.136
cardiovascular system	0.0 (0.0 – 4.0)	0.0 (0.0 – 2.0)	0.0 (-1.5 – 0.0)	0.566
digestive system	4.0 (0.0 – 8.5)	1.5 (0.0 – 7.0)	0.0 (-2.0 – 2.5)	0.893
frequency of defecation	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.25)	0.0 (0.0 – 0.32)	0.133
musculoskeletal system	5.0 (2.5 – 14.0)	4.5 (1.0 – 9.0)	-0.5 (-3.5 – 1.5)	0.163
urinary system	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.50
gynecological impairment	4.0 (0.0 – 5.5)	2.5 (0.0 – 10.5)	0.0 (-1.5 – 2.0)	0.938
total scale	22.5 (13.5 – 41.5)	20.0 (5.0 – 36.0)	-5.0 (-9.0 – 5.5)	0.425

*IQR=inter quartile range

The results in Table 10 allow the conclusion that there was no change in potential complaints during the participation of the study. Additionally, the change in feeling since the start of the study (question 2 of the questionnaire) was answered with a median of 3.0, which means “no change”. The inter quartile range is from 2.0 to 3.0. Hence, the occurrence of potential complaints associated with the administration of soya drugs can not be concluded.

The medians and respective inter quartile ranges of the subscales and the results of the WILCOXON signed rank tests for the participants randomized to the treatment sequence 1 are summarized in Table 11. The medians and respective inter quartile ranges of the subscales and the results of the WILCOXON signed rank tests for the participants randomized to the treatment sequence 1 are summarized in Table 12.

Table 11: Median and inter quartile ranges of the subscales at the beginning and at the end of the study, for the difference, and results from the WILCOXON signed rank tests for the subjects randomized to treatment sequence 1.

scale	begin of study (median (IQR*))	end of study (median (IQR*))	difference in the score (median (IQR*))	p-value
general wellbeing	14.0 (9.0 – 21.0)	12.5 (3.0 – 27.0)	-1.5 (-5.0 – 1.0)	0.316
cardiovascular system	0.5 (0.0 – 4.0)	1.5 (0.0 – 4.0)	0.0 (-1.0 – 2.0)	0.719
digestive system	6.5 (3.0 – 10.0)	6.5 (0.0 – 8.0)	-1.0 (-2.0 – 6.0)	0.947
frequency of defecation	1.0 (0.57 – 1.0)	1.0 (1.0 – 1.0)	0.0 (0.0 – 0.14)	0.375
musculoskeletal system	7.0 (5.0 – 18.0)	8.5 (6.0 – 14.0)	0.5 (-4.0 – 2.0)	0.688
urinary system	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.500
gynecological impairment	4.0 (0.0 – 5.0)	3.0 (0.0 – 11.0)	0.0 (-3.0 – 3.0)	0.938
total scale	39.0 (15.0 – 72.0)	29.0 (18.0 – 65.0)	-1.5 (-9.0 – 8.0)	0.846

*IQR=inter quartile range

Table 12: Median and inter quartile ranges of the subscales at the beginning and at the end of the study, for the difference, and results from the WILCOXON signed rank tests for the subjects randomized to treatment sequence 2.

scale	begin of study (median (IQR*))	end of study (median (IQR*))	difference in the score (median (IQR*))	p-value
general wellbeing	6.5 (5.0 – 10.0)	4.0 (2.0 – 8.0)	-3.5 (-4.0 – 1.0)	0.436
cardiovascular system	0.0 (0.0 – 4.0)	0.0 (0.0 – 0.0)	0.0 (-2.0 – 0.0)	0.125
digestive system	0.0 (0.0 – 5.0)	0.0 (0.0 – 3.0)	0.0 (0.0 – 0.0)	1.00
frequency of defecation	1.0 (1.0 – 1.5)	1.0 (1.0 –1.5)	0.0 (0.0 – 0.50)	0.375
musculoskeletal system	2.5 (1.0 – 8.0)	1.5 (0.0 – 3.0)	-1.5 (-3.0 – 1.0)	0.121
urinary system	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	-**
gynecological impairment	3.5 (0.0 – 6.0)	1.0 (0.0 – 10.0)	0.0 (0.0 – 0.0)	1.000
total scale	14.0 (10.0 – 26.0)	7.0 (3.0 – 22.0)	-5.0 (-9.0 – 2.0)	0.359

*IQR=inter quartile range.
** WILCOXON signed rank tests could not performed because all differences are 0.

The results in Table 11 and Table 12 suggest that changes in potential complaints in each treatment sequence during the participation of the study can not be concluded. Furthermore, the change in feeling since the start of the study (question 2 of the questionnaire) was answered in each treatment sequence with a median of 3.0, which means “no change”. The inter quartile range is from 2.0 to 3.0.

6 Conclusions

Bioequivalence of the parameters $AUC_{0\rightarrow 24}$, $c\_max_{0\rightarrow 24}$, $t\_max_{0\rightarrow 24}$:

The results allow the conclusion that there is no bioequivalence for the capsule and the tablet formulation (see Table 6 and Table 7). Both, the $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$ are higher for the capsule formulation. Thus, after unique administration of the drug, the amount of absorbed isoflavones and the maximum concentration of isoflavones are higher for the capsule formulation. Corresponding to the retarded availability of isoflavones from the tablet formulation, the parameter $t\_max_{0\rightarrow 24}$ (which indicates the time at which the maximum concentration is reached) is lower for the capsule formulation. Hence, the present data show a tendency for a faster availability of isoflavones for the capsule formulation after unique administration.

Residual availability of the parameters AUC_{res}, c_max_{res}, t_max_{res}:

The analyses suggest no difference in the parameters of interest between the capsule and the tablet formulation. During the phase of daily administration of the drug (28 days) in period II, differences between capsule and tablet in the residual availability could not be concluded.

Investigation of potential complaints:

The results show that there was no change in potential complaints in the whole study population during the participation of the study. Neither in treatment sequence 1 nor in treatment sequence 2 are remarkable changes in any subscale investigated. Hence, with respect of the long washing out phase of 14 days, neither the administration of the tablet nor the administration of the capsule shows an influence on the potential complaints investigated.

7 References

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8 Appendix

8.1 List of Tables

Legend for Table A 1:

snr: screening number
Sequence: treatment sequence (C T = treatment sequence 1, T C = treatment sequence 2)
period I: formulation, which was administered in period I (C = capsule, T = tablet)
period II: formulation, which was administered in period II (C = capsule, T = tablet)

Legend for Table A 2, Table A 3, Table A 4, Table A 5, Table A 6, Table A 7, Table A 8, and Table A 9:

snr: screening number
Seq.: treatment sequence (C T = treatment sequence 1, T C = treatment sequence 2)
Period: period (C = capsule, T = tablet)
t. 0.0: time point (h) at which the baseline measurement was taken
t. 0.5: time point (h) at which the measurement at 0.5 hours after drug administration was taken
t. 1.0: time point (h) at which the measurement at 1 hour after drug administration was taken
t. 2.0: time point (h) at which the measurement at 2 hours after drug administration was taken
t. 3.0: time point (h) at which the measurement at 3 hours after drug administration was taken
t. 6.0: time point (h) at which the measurement at 6 hours after drug administration was taken
t. 12.0: time point (h) at which the measurement at 12 hours after drug administration was taken
t. 24.0: time point (h) at which the measurement at 24 hours after drug administration was taken
M. 0.0: drug concentration (nMol/l) at baseline
M. 0.5: drug concentration (nMol/l) at 0.5 hours after drug administration
M. 1.0: drug concentration (nMol/l) at 1 hour after drug administration
M. 2.0: drug concentration (nMol/l) at 2 hours after drug administration
M. 3.0: drug concentration (nMol/l) at 3 hours after drug administration
M. 6.0: drug concentration (nMol/l) at 6 hours after drug administration
M. 12.0: drug concentration (nMol/l) at 12 hours after drug administration
M. 24.0: drug concentration (nMol/l) at 24 hours after drug administration
STD: standard deviation
CV: coefficient of variation

Legend for Table A 10, Table A 11, Table A 12, Table A 13, Table A 14, Table A 15, Table A 16, and Table A 17:

snr: screening number
Seq.: treatment sequence (C T = treatment sequence 1, T C = treatment sequence 2)
Period: period (C = capsule, T = tablet)
Tp. 1: time point (d) at which the residual concentration at the end of day 1 in period II was taken
Tp. 4: time point (d) at which the residual concentration at the beginning of day 4 in period II was taken
Tp. 8: time point (d) at which the residual concentration at the beginning of day 8 in period II was taken
Tp. 15: time point (d) at which the residual concentration at the beginning of day 15 in period II was taken
Tp. 29: time point (d) at which the residual concentration at the beginning of day 29 in period II was taken
Day 1: residual drug concentration (nMol/l) at the end of day 1 in period II
Day 4: residual drug concentration (nMol/l) at the beginning of day 3 in period II
Day 8: residual drug concentration (nMol/l) at the beginning of day 7 in period II
Day 15: residual drug concentration (nMol/l) at the beginning of day 14 in period II
Day 29: residual drug concentration (nMol/l) at the beginning of day 28 in period II
STD: standard deviation
CV: coefficient of variation

All measurements were taken at the end of the days 1, 3, 7, 14, and 28. The labels “Day 1” and “Tp. 1” denote the measurement and the first time point. The labels “Day 4”, “Day 8”, “Day 15”, “Day 29” and “Tp. 1”, “Tp. 4”, “Tp. 8”, “Tp. 15”, “Tp. 29” denote the time points and measurements at the beginning of the days 4, 8, 15, and 29, which are equal to the end of the days 3, 7, 14, 28.

Legend for Table A 18, Table A 19,
Table A 20, Table A 21, Table A 22, and Table A 23:

snr: screening number
Seq.: treatment sequence (C T = treatment sequence 1, T C = treatment sequence 2)
Period: period (C = capsule, T = tablet)
$AUC_{0\rightarrow 24}$: area under the raw concentration versus time curve over the interval 0 to 24 hours (nMol/l*day)
$c\_max_{0\rightarrow 24}$: maximum observed concentration (nMol/l)
$t\_max_{0\rightarrow 24}$: sampling time at which $c\_max_{0\rightarrow 24}$ occurred (h)
*: for the parameter $t\_max_{0\rightarrow 24}$, the median instead of the mean was calculated

Legend for Table A 24, Table A 25, Table A 26, Table A 27, Table A 28, Table A 29, Table A 30, and Table A 31:

snr: screening number
Seq.: treatment sequence (C T = treatment sequence 1, T C = treatment sequence 2)
Period: period (C = capsule, T = tablet)
AUC_{res}: area under the raw residual concentration versus time curve over the interval 1 to 28 days in period II (nMol/l*day)
c_max_{res}: maximum observed concentration in period II (nMol/l)
t_max_{res}: sampling time at which c_max_{res} occurred (day)
STD: standard deviation
CV: coefficient of variation
*: for the parameter t_max_{res}, the median instead of the mean was calculated
STD: standard deviation
CV: coefficient of variation

Legend for Table A 41, Table A 42, Table A 43, Table A 44, Table A 45, Table A 46, Table A 47, Table A 48, and Table A 49:

snr: screening number
Seq.: treatment sequence (C T = treatment sequence 1, T C = treatment sequence 2)
*: for the parameter t_max_{res}, the median instead of the mean was calculated
STD: standard deviation
CV: coefficient of variation

Table A 1: Randomization scheme of the cross over design for comparison of tablet versus capsule formulation.

snr	Date of Randomization	Sequence	period I	period II
1	14/06/2004	T C	T[+]	C
2	15/06/2004	T C	T	C
3	14/06/2004	T C	T	C
4	15/06/2004	T C	*	*
5	15/06/2004	C T	C	T
6	14/06/2004	C T	C	T
7	15/06/2004	T C	T	C
8	15/06/2004	C T	C	T
9	15/06/2004	T C	T	C
10	15/06/2004	C T	C	T
11	15/06/2004	C T	C	T
12	21/06/2004	C T	C	T
13	16/06/2004	T C	T	C
14	16/06/2004	T C	T	C
15	21/06/2004	C T	C	T
16	21/06/2004	C T	C	**
17	21/06/2004	T C	T	C
18	19/07/2004	T C	T	C
19	19/07/2004	C T	C	T
20	26/07/2004	T C	T	C
21	19/07/2004	C T	C	T
22	28/07/2004	C T	C	T
23	09/08/2004	C T	C	**

[+] no measurements are available for period I
* screening number 4: drop out after randomization.
** screening number 16, and 23: drop out after finishing period I of the study.

Table A 2: Concentration of daidzein for each subject given the tablet formulation.

snr	Seq.	Period	t. 0.0	M. 0.0	t. 0.5	M. 0.5	t. 1.0	M. 1.0	t. 2.0	M. 2.0	t. 3.0	M. 3.0	t. 6.0	M. 6.0	t. 12.0	M. 12.0	t. 24.0	M. 24.0
1	T C	T	-48.00	6.90	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2	T C	T	-4.00	0.00	0.75	39.60	1.17	39.50	2.25	41.40	3.00	99.40	6.00	125.10	11.92	52.10	24.00	16.90
3	T C	T	-96.00	0.00	0.50	15.10	1.00	14.10	2.00	43.20	3.00	50.10	6.00	42.50	11.92	151.30	24.50	9.10
4	T C	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	C T	T	-0.08	0.00	0.50	25.00	1.17	52.00	2.08	73.00	3.08	47.00	6.02	145.00	11.50	229.00	23.93	81.00
6	C T	T	-0.08	0.00	0.53	0.00	1.05	0.00	2.07	0.00	3.25	6.00	6.05	43.00	14.00	118.00	24.08	41.00
7	T C	T	-0.07	0.00	0.50	11.80	1.00	40.00	2.00	33.70	3.00	36.00	5.52	264.50	11.75	122.00	24.00	8.70
8	C T	T	-0.08	0.00	0.58	3.00	1.05	14.00	2.00	16.00	3.08	28.00	6.08	47.00	11.92	14.00	24.33	0.00
9	T C	T	-96.00	0.00	0.50	12.30	1.00	57.30	2.00	33.60	3.00	115.50	6.08	343.20	11.92	187.20	23.92	46.60
10	C T	T	-0.08	15.00	.	.	1.25	0.00	2.25	0.00	3.25	0.00	6.25	4.00	11.83	6.00	25.08	45.00
11	C T	T	-0.02	0.00	0.50	5.00	1.58	7.00	2.08	10.00	3.12	17.00	6.08	21.00	11.62	70.00	25.00	14.00
12	C T	T	-0.02	9.00	0.68	27.00	1.15	55.00	2.00	69.00	3.12	84.00	5.65	87.00	12.23	71.00	24.57	24.00
13	T C	T	-0.33	0.00	0.53	29.10	1.08	32.10	2.25	27.10	3.25	33.40	6.33	278.20	12.08	107.40	24.13	11.10
14	T C	T	-0.03	35.70	0.63	72.80	1.12	19.00	2.05	0.00	3.05	16.90	6.13	185.00	11.72	216.50	24.00	31.40
15	C T	T	-0.02	0.00	0.68	33.00	1.23	21.00	2.18	23.00	3.32	228.00	6.12	43.00	12.07	83.00	23.98	19.00
16	C T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	T C	T	-0.08	0.00	0.45	0.00	1.08	9.00	2.08	98.00	3.08	52.00	6.10	90.00	11.92	130.00	24.00	6.00
18	T C	T	-0.17	0.00	0.62	35.00	1.00	377.00	1.97	198.00	3.00	271.00	6.17	55.00	11.68	319.00	26.17	9.00
19	C T	T	-0.02	0.00	0.50	16.00	1.00	39.00	2.00	28.00	2.92	23.00	6.07	253.00	11.58	193.00	26.25	35.00
20	T C	T	-0.03	0.00	0.50	17.00	1.02	30.00	2.05	295.00	3.08	282.00	6.17	538.00	11.72	256.00	23.88	25.00
21	C T	T	-0.02	0.00	0.50	2.00	1.03	30.00	2.00	61.00	3.00	30.00	6.05	51.00	11.85	7.00	24.07	0.00
22	C T	T	-0.03	0.00	0.50	0.00	1.02	0.00	2.03	5.00	3.00	28.00	6.05	66.00	11.60	37.00	23.95	4.00
23	C T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Mean			-12.26	3.33	0.55	19.09	1.11	44.00	2.07	55.53	3.08	76.17	6.05	141.13	11.94	124.71	24.41	22.46
STD			30.56	8.60	0.08	18.66	0.14	82.73	0.09	74.29	0.11	87.69	0.18	138.42	0.53	89.67	0.72	20.44
CV				258.36	15.15	97.74	12.71	188.02	4.50	133.79	3.57	115.12	3.05	98.08	4.47	71.90	2.97	91.00

Table A 3: Concentration of genistein for each subject given the tablet formulation.

snr	Seq.	Period	t. 0.0	M. 0.0	t. 0.5	M. 0.5	t. 1.0	M. 1.0	t. 2.0	M. 2.0	t. 3.0	M. 3.0	t. 6.0	M. 6.0	t. 12.0	M. 12.0	t. 24.0	M. 24.0
1	T C	T	-48.00	38.60	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2	T C	T	-4.00	16.10	0.75	123.20	1.17	99.00	2.25	115.10	3.00	194.90	6.00	248.80	11.92	195.00	24.00	112.50
3	T C	T	-96.00	6.40	0.50	27.70	1.00	30.70	2.00	114.50	3.00	1526.60	6.00	194.10	11.92	163.30	24.50	32.60
4	T C	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	C T	T	-0.08	49.00	0.50	55.00	1.17	154.00	2.08	278.00	3.08	246.00	6.02	578.00	11.50	773.00	23.93	475.00
6	C T	T	-0.08	0.00	0.53	0.00	1.05	25.00	2.07	31.00	3.25	30.00	6.05	239.00	14.00	612.00	24.08	654.00
7	T C	T	-0.07	7.80	0.50	25.80	1.00	103.30	2.00	107.60	3.00	144.70	5.52	611.90	11.75	279.90	24.00	177.50
8	C T	T	-0.08	0.00	0.58	7.00	1.05	44.00	2.00	54.00	3.08	90.00	6.08	105.00	11.92	57.00	24.33	23.00
9	T C	T	-96.00	10.00	0.50	34.00	1.00	129.80	2.00	96.80	3.00	324.70	6.08	617.20	11.92	527.30	23.92	281.60
10	C T	T	-0.08	84.00	.	.	1.25	0.00	2.25	0.00	3.25	7.00	6.25	14.00	11.83	27.00	25.08	156.00
11	C T	T	-0.02	0.00	0.50	13.00	1.58	22.00	2.08	27.00	3.12	40.00	6.08	86.00	11.62	83.00	25.00	29.00
12	C T	T	-0.02	66.00	0.68	194.00	1.15	302.00	2.00	428.00	3.12	508.00	5.65	572.00	12.23	432.00	24.57	378.00
13	T C	T	-0.33	15.70	0.53	65.40	1.08	98.20	2.25	95.90	3.25	108.30	6.33	422.70	12.08	358.00	24.13	177.20
14	T C	T	-0.03	115.30	0.63	144.50	1.12	38.00	2.05	109.00	3.05	28.30	6.13	119.40	11.72	221.80	24.00	106.10
15	C T	T	-0.02	18.00	0.68	79.00	1.23	80.00	2.18	79.00	3.32	566.00	6.12	240.00	12.07	339.00	23.98	182.00
16	C T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	T C	T	-0.08	10.00	0.45	25.00	1.08	30.00	2.08	503.00	3.08	304.00	6.10	280.00	11.92	361.00	24.00	150.00
18	T C	T	-0.17	13.00	0.62	59.00	1.00	1136.00	1.97	575.00	3.00	1000.00	6.17	98.00	11.68	1381.00	26.17	219.00
19	C T	T	-0.02	76.00	0.50	69.00	1.00	164.00	2.00	158.00	2.92	133.00	6.07	514.00	11.58	433.00	26.25	153.00
20	T C	T	-0.03	15.00	0.50	59.00	1.02	117.00	2.05	959.00	3.08	1190.00	6.17	632.00	11.72	618.00	23.88	133.00
21	C T	T	-0.02	0.00	0.50	7.00	1.03	100.00	2.00	214.00	3.00	146.00	6.05	215.00	11.85	77.00	24.07	22.00
22	C T	T	-0.03	0.00	0.50	0.00	1.02	0.00	2.03	14.00	3.00	67.00	6.05	149.00	11.60	70.00	23.95	32.00
23	C T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Mean			-12.26	27.05	0.55	54.87	1.11	140.68	2.07	208.36	3.08	350.24	6.05	312.43	11.94	368.86	24.41	183.87
STD			30.56	33.46	0.08	53.28	0.14	251.62	0.09	245.98	0.11	433.23	0.18	211.86	0.53	326.22	0.72	165.49
CV				123.71	15.15	97.10	12.71	178.86	4.50	118.05	3.57	123.70	3.05	67.81	4.47	88.44	2.97	90.00

Table A 4: Concentration of equol for each subject given the tablet formulation.

snr	Seq.	Period	t. 0.0	M. 0.0	t. 0.5	M. 0.5	t. 1.0	M. 1.0	t. 2.0	M. 2.0	t. 3.0	M. 3.0	t. 6.0	M. 6.0	t. 12.0	M. 12.0	t. 24.0	M. 24.0
1	T C	T	-48.00	0.00	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2	T C	T	-4.00	0.00	0.75	0.00	1.17	0.00	2.25	0.00	3.00	0.00	6.00	0.00	11.92	0.00	24.00	0.00
3	T C	T	-96.00	0.00	0.50	0.00	1.00	0.00	2.00	0.00	3.00	0.00	6.00	0.00	11.92	0.00	24.50	0.00
4	T C	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	C T	T	-0.08	0.00	0.50	0.00	1.17	0.00	2.08	0.00	3.08	0.00	6.02	0.00	11.50	0.00	23.93	0.00
6	C T	T	-0.08	0.00	0.53	0.00	1.05	0.00	2.07	0.00	3.25	0.00	6.05	0.00	14.00	0.00	24.08	0.00
7	T C	T	-0.07	0.00	0.50	0.00	1.00	0.00	2.00	0.00	3.00	0.00	5.52	0.00	11.75	0.00	24.00	0.00
8	C T	T	-0.08	0.00	0.58	0.00	1.05	0.00	2.00	0.00	3.08	0.00	6.08	0.00	11.92	0.00	24.33	0.00
9	T C	T	-96.00	0.00	0.50	0.00	1.00	0.00	2.00	0.00	3.00	0.00	6.08	0.00	11.92	0.00	23.92	0.00
10	C T	T	-0.08	0.00	.	.	1.25	0.00	2.25	0.00	3.25	0.00	6.25	0.00	11.83	0.00	25.08	0.00
11	C T	T	-0.02	0.00	0.50	0.00	1.58	0.00	2.08	0.00	3.12	0.00	6.08	0.00	11.62	0.00	25.00	0.00
12	C T	T	-0.02	0.00	0.68	0.00	1.15	0.00	2.00	0.00	3.12	0.00	5.65	0.00	12.23	0.00	24.57	0.00
13	T C	T	-0.33	0.00	0.53	0.00	1.08	0.00	2.25	0.00	3.25	0.00	6.33	0.00	12.08	0.00	24.13	0.00
14	T C	T	-0.03	0.00	0.63	0.00	1.12	0.00	2.05	0.00	3.05	0.00	6.13	0.00	11.72	0.00	24.00	0.00
15	C T	T	-0.02	0.00	0.68	0.00	1.23	0.00	2.18	0.00	3.32	0.00	6.12	0.00	12.07	0.00	23.98	0.00
16	C T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	T C	T	-0.08	0.00	0.45	0.00	1.08	0.00	2.08	0.00	3.08	0.00	6.10	0.00	11.92	0.00	24.00	0.00
18	T C	T	-0.17	0.00	0.62	0.00	1.00	0.00	1.97	0.00	3.00	0.00	6.17	0.00	11.68	0.00	26.17	0.00
19	C T	T	-0.02	0.00	0.50	0.00	1.00	0.00	2.00	0.00	2.92	0.00	6.07	0.00	11.58	0.00	26.25	0.00
20	T C	T	-0.03	0.00	0.50	0.00	1.02	0.00	2.05	0.00	3.08	0.00	6.17	0.00	11.72	0.00	23.88	0.00
21	C T	T	-0.02	0.00	0.50	0.00	1.03	0.00	2.00	0.00	3.00	0.00	6.05	0.00	11.85	0.00	24.07	0.00
22	C T	T	-0.03	0.00	0.50	0.00	1.02	0.00	2.03	0.00	3.00	0.00	6.05	0.00	11.60	0.00	23.95	0.00
23	C T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Mean			-12.26	0.00	0.55	0.00	1.11	0.00	2.07	0.00	3.08	0.00	6.05	0.00	11.94	0.00	24.41	0.00
STD			30.56	0.00	0.08	0.00	0.14	0.00	0.09	0.00	0.11	0.00	0.18	0.00	0.53	0.00	0.72	0.00
CV					15.15		12.71		4.50		3.57		3.05		4.47		2.97	

Table A 5: Concentration of total sum of isoflavones for each subject given the tablet formulation.

snr	Seq.	Period	t. 0.0	M. 0.0	t. 0.5	M. 0.5	t. 1.0	M. 1.0	t. 2.0	M. 2.0	t. 3.0	M. 3.0	t. 6.0	M. 6.0	t. 12.0	M. 12.0	t. 24.0	M. 24.0
1	T C	T	-48.00	45.50	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2	T C	T	-4.00	16.10	0.75	162.80	1.17	138.50	2.25	156.50	3.00	294.30	6.00	373.90	11.92	247.10	24.00	129.40
3	T C	T	-96.00	6.40	0.50	42.80	1.00	44.80	2.00	157.70	3.00	1576.70	6.00	236.60	11.92	314.60	24.50	41.70
4	T C	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	C T	T	-0.08	49.00	0.50	80.00	1.17	206.00	2.08	351.00	3.08	293.00	6.02	723.00	11.50	1002.00	23.93	556.00
6	C T	T	-0.08	0.00	0.53	0.00	1.05	25.00	2.07	31.00	3.25	36.00	6.05	282.00	14.00	730.00	24.08	695.00
7	T C	T	-0.07	7.80	0.50	37.60	1.00	143.30	2.00	141.30	3.00	180.70	5.52	876.40	11.75	401.90	24.00	186.20
8	C T	T	-0.08	0.00	0.58	10.00	1.05	58.00	2.00	70.00	3.08	118.00	6.08	152.00	11.92	71.00	24.33	23.00
9	T C	T	-96.00	10.00	0.50	46.30	1.00	187.10	2.00	130.40	3.00	440.20	6.08	960.40	11.92	714.50	23.92	328.20
10	C T	T	-0.08	99.00	.	.	1.25	0.00	2.25	0.00	3.25	7.00	6.25	18.00	11.83	33.00	25.08	201.00
11	C T	T	-0.02	0.00	0.50	18.00	1.58	29.00	2.08	37.00	3.12	57.00	6.08	107.00	11.62	153.00	25.00	43.00
12	C T	T	-0.02	75.00	0.68	221.00	1.15	357.00	2.00	497.00	3.12	592.00	5.65	659.00	12.23	503.00	24.57	402.00
13	T C	T	-0.33	15.70	0.53	94.50	1.08	130.30	2.25	123.00	3.25	141.70	6.33	700.90	12.08	465.40	24.13	188.30
14	T C	T	-0.03	151.00	0.63	217.30	1.12	57.00	2.05	109.00	3.05	45.20	6.13	304.40	11.72	438.30	24.00	137.50
15	C T	T	-0.02	18.00	0.68	112.00	1.23	101.00	2.18	102.00	3.32	794.00	6.12	283.00	12.07	422.00	23.98	201.00
16	C T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	T C	T	-0.08	10.00	0.45	25.00	1.08	39.00	2.08	601.00	3.08	356.00	6.10	370.00	11.92	491.00	24.00	156.00
18	T C	T	-0.17	13.00	0.62	94.00	1.00	1513.00	1.97	773.00	3.00	1271.00	6.17	153.00	11.68	1700.00	26.17	228.00
19	C T	T	-0.02	76.00	0.50	85.00	1.00	203.00	2.00	186.00	2.92	156.00	6.07	767.00	11.58	626.00	26.25	188.00
20	T C	T	-0.03	15.00	0.50	76.00	1.02	147.00	2.05	1254.00	3.08	1472.00	6.17	1170.00	11.72	874.00	23.88	158.00
21	C T	T	-0.02	0.00	0.50	9.00	1.03	130.00	2.00	275.00	3.00	176.00	6.05	266.00	11.85	84.00	24.07	22.00
22	C T	T	-0.03	0.00	0.50	0.00	1.02	0.00	2.03	19.00	3.00	95.00	6.05	215.00	11.60	107.00	23.95	36.00
23	C T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Mean			-12.26	30.38	0.55	73.96	1.11	184.68	2.07	263.89	3.08	426.41	6.05	453.56	11.94	493.57	24.41	206.33
STD			30.56	40.75	0.08	68.74	0.14	333.69	0.09	317.97	0.11	495.82	0.18	328.93	0.53	402.43	0.72	179.77
CV				134.15	15.15	92.94	12.71	180.68	4.50	120.49	3.57	116.28	3.05	72.52	4.47	81.53	2.97	87.13

Table A 6: Concentration of daidzein for each subject given the capsule formulation.

snr	Seq.	Period	t. 0.0	M. 0.0	t. 0.5	M. 0.5	t. 1.0	M. 1.0	t. 2.0	M. 2.0	t. 3.0	M. 3.0	t. 6.0	M. 6.0	t. 12.0	M. 12.0	t. 24.0	M. 24.0
1	T C	C	-0.03	0.00	0.50	9.00	1.00	62.00	2.00	167.00	3.05	112.00	6.17	201.00	12.00	87.00	24.00	12.00
2	T C	C	-0.08	0.00	0.62	176.00	1.07	529.00	2.07	468.00	3.08	298.00	6.32	487.00	11.58	78.00	24.08	11.00
3	T C	C	-0.05	0.00	0.58	737.00	1.08	568.00	2.08	304.00	3.08	222.00	6.08	120.00	12.08	259.00	24.08	47.00
4	T C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	C T	C	-96.00	0.00	0.50	66.80	1.00	184.30	2.00	104.00	3.00	82.50	6.00	206.30	11.83	73.70	24.25	33.10
6	C T	C	-0.25	60.80	0.50	29.20	1.00	67.00	2.00	182.00	3.00	122.00	6.00	255.90	12.45	142.90	27.00	16.60
7	T C	C	-0.03	0.00	0.50	229.00	1.05	278.00	2.05	268.00	3.05	314.00	6.00	40.00	11.80	5.00	23.97	0.00
8	C T	C	-0.07	0.00	0.50	516.00	1.08	446.70	2.08	143.40	3.12	1074.10	6.17	65.10	11.83	29.60	23.78	0.00
9	T C	C	-0.08	0.00	0.45	79.00	0.92	54.00	2.00	275.00	2.92	64.00	6.00	62.00	12.00	28.00	23.93	6.00
10	C T	C	-24.00	0.00	0.50	292.70	1.00	103.10	2.00	123.10	3.00	133.10	6.08	104.20	11.92	227.90	23.92	23.80
11	C T	C	-0.02	0.00	0.75	359.90	1.12	359.20	2.12	113.40	3.25	510.20	6.17	200.10	12.00	111.90	24.83	27.80
12	C T	C	-0.17	0.00	0.53	5.50	1.08	32.10	2.05	330.20	3.05	235.20	5.97	168.00	11.97	45.00	23.92	35.00
13	T C	C	-0.08	0.00	0.58	532.00	1.00	684.00	2.17	156.00	3.17	103.00	6.08	194.00	12.17	107.00	24.25	9.00
14	T C	C	-0.08	0.00	0.58	382.00	1.05	283.00	2.02	171.00	3.08	94.00	6.13	274.00	11.92	50.00	24.00	9.00
15	C T	C	-0.05	11.10	0.45	161.80	0.88	88.10	2.17	54.70	3.33	227.10	6.13	260.50	12.07	100.50	24.08	9.50
16	C T	C	-0.08	0.00	0.57	133.00	1.05	195.00	2.05	521.00	3.00	315.00	6.00	230.00	11.97	83.00	24.13	21.00
17	T C	C	-0.20	0.00	0.50	81.00	1.63	192.00	2.38	171.00	3.13	263.00	5.90	373.00	11.63	69.00	23.47	7.00
18	T C	C	-0.08	0.00	0.50	348.00	1.02	786.00	2.00	359.00	3.00	479.00	6.02	177.00	11.92	107.00	26.42	9.00
19	C T	C	-0.03	0.00	0.50	27.00	0.95	234.00	1.97	199.00	3.00	115.00	6.12	378.00	11.58	100.00	26.13	13.00
20	T C	C	-0.02	0.00	0.50	31.00	1.05	84.00	2.10	65.00	3.02	35.00	6.07	119.00	11.73	31.00	23.82	6.00
21	C T	C	-0.05	0.00	0.55	17.00	1.00	742.00	2.00	604.00	3.02	573.00	6.03	299.00	11.67	91.00	23.95	0.00
22	C T	C	-0.03	0.00	0.50	58.00	1.00	124.00	2.00	542.00	3.00	368.00	6.00	641.00	11.47	119.00	23.97	14.00
23	C T	C	-0.03	0.00	0.50	62.00	1.02	192.00	2.00	554.00	3.12	190.00	6.13	395.00	11.72	74.00	24.00	6.00
Mean			-5.52	3.27	0.53	196.95	1.05	285.80	2.06	267.04	3.07	269.51	6.07	238.64	11.88	91.80	24.36	14.35
STD			20.84	13.07	0.07	204.24	0.14	237.17	0.09	171.13	0.09	233.73	0.09	146.91	0.23	59.92	0.92	12.29
CV				399.78	12.32	103.70	13.49	82.99	4.43	64.08	3.03	86.72	1.52	61.56	1.89	65.28	3.77	85.63

Table A 7: Concentration of genistein for each subject given the capsule formulation.

snr	Seq.	Period	t. 0.0	M. 0.0	t. 0.5	M. 0.5	t. 1.0	M. 1.0	t. 2.0	M. 2.0	t. 3.0	M. 3.0	t. 6.0	M. 6.0	t. 12.0	M. 12.0	t. 24.0	M. 24.0
1	T C	C	-0.03	24.00	0.50	29.00	1.00	119.00	2.00	451.00	3.05	455.00	6.17	602.00	12.00	545.00	24.00	286.00
2	T C	C	-0.08	0.00	0.62	265.00	1.07	1058.00	2.07	1575.00	3.08	1372.00	6.32	1496.00	11.58	744.00	24.08	360.00
3	T C	C	-0.05	35.00	0.58	1333.00	1.08	1398.00	2.08	1102.00	3.08	1004.00	6.08	828.00	12.08	731.00	24.08	284.00
4	T C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	C T	C	-96.00	9.70	0.50	97.00	1.00	481.40	2.00	416.30	3.00	394.50	6.00	719.10	11.83	487.20	24.25	229.80
6	C T	C	-0.25	196.90	0.50	81.80	1.00	230.50	2.00	593.40	3.00	522.10	6.00	1269.70	12.45	1172.20	27.00	752.10
7	T C	C	-0.03	32.00	0.50	283.00	1.05	585.00	2.05	1038.00	3.05	998.00	6.00	135.00	11.80	101.00	23.97	26.00
8	C T	C	-0.07	0.00	0.50	926.20	1.08	1391.10	2.08	652.50	3.12	503.40	6.17	183.00	11.83	241.20	23.78	89.20
9	T C	C	-0.08	0.00	0.45	84.00	0.92	102.00	2.00	85.00	2.92	195.00	6.00	147.00	12.00	141.00	23.93	60.00
10	C T	C	-24.00	9.20	0.50	919.70	1.00	322.30	2.00	527.00	3.00	332.70	6.08	288.30	11.92	512.60	23.92	189.80
11	C T	C	-0.02	17.50	0.75	385.20	1.12	550.90	2.12	269.80	3.25	1004.70	6.17	348.30	12.00	338.00	24.83	113.00
12	C T	C	-0.17	81.50	0.53	90.30	1.08	128.50	2.05	877.40	3.05	984.50	5.97	723.20	11.97	423.10	23.92	422.70
13	T C	C	-0.08	17.00	0.58	1013.00	1.00	1434.00	2.17	751.00	3.17	585.00	6.08	722.00	12.17	482.00	24.25	314.00
14	T C	C	-0.08	66.00	0.58	969.00	1.05	984.00	2.02	861.00	3.08	703.00	6.13	651.00	11.92	278.00	24.00	102.00
15	C T	C	-0.05	132.90	0.45	218.50	0.88	209.70	2.17	174.30	3.33	396.10	6.13	627.50	12.07	547.40	24.08	208.90
16	C T	C	-0.08	0.00	0.57	199.00	1.05	389.00	2.05	1334.00	3.00	664.00	6.00	751.00	11.97	437.00	24.13	317.00
17	T C	C	-0.20	45.00	0.50	124.00	1.63	584.00	2.38	537.00	3.13	536.00	5.90	1017.00	11.63	419.00	23.47	199.00
18	T C	C	-0.08	36.00	0.50	346.00	1.02	163.00	2.00	1412.00	3.00	1694.00	6.02	922.00	11.92	675.00	26.42	154.00
19	C T	C	-0.03	16.00	0.50	40.00	0.95	410.00	1.97	668.00	3.00	498.00	6.12	780.00	11.58	378.00	26.13	170.00
20	T C	C	-0.02	0.00	0.50	73.00	1.05	209.00	2.10	292.00	3.02	214.00	6.07	197.00	11.73	136.00	23.82	38.00
21	C T	C	-0.05	0.00	0.55	14.00	1.00	1072.00	2.00	1438.00	3.02	1577.00	6.03	1058.00	11.67	787.00	23.95	1867.00
22	C T	C	-0.03	23.00	0.50	87.00	1.00	228.00	2.00	1509.00	3.00	1400.00	6.00	1441.00	11.47	579.00	23.97	145.00
23	C T	C	-0.03	9.00	0.50	32.00	1.02	199.00	2.00	1381.00	3.12	799.00	6.13	1044.00	11.72	679.00	24.00	248.00
Mean			-5.52	34.12	0.53	345.90	1.05	556.75	2.06	815.67	3.07	765.09	6.07	725.00	11.88	492.44	24.36	298.89
STD			20.84	48.60	0.07	401.34	0.14	452.79	0.09	467.96	0.09	436.15	0.09	400.73	0.23	250.15	0.92	384.21
CV				142.43	12.32	116.03	13.49	81.33	4.43	57.37	3.03	57.01	1.52	55.27	1.89	50.80	3.77	128.55

Table A 8: Concentration of equol for each subject given the capsule formulation.

snr	Seq.	Period	t. 0.0	M. 0.0	t. 0.5	M. 0.5	t. 1.0	M. 1.0	t. 2.0	M. 2.0	t. 3.0	M. 3.0	t. 6.0	M. 6.0	t. 12.0	M. 12.0	t. 24.0	M. 24.0
1	T C	C	-0.03	0.00	0.50	0.00	1.00	0.00	2.00	0.00	3.05	0.00	6.17	0.00	12.00	0.00	24.00	0.00
2	T C	C	-0.08	0.00	0.62	0.00	1.07	0.00	2.07	0.00	3.08	0.00	6.32	0.00	11.58	0.00	24.08	0.00
3	T C	C	-0.05	0.00	0.58	0.00	1.08	0.00	2.08	0.00	3.08	0.00	6.08	0.00	12.08	0.00	24.08	0.00
4	T C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	C T	C	-96.00	0.00	0.50	0.00	1.00	0.00	2.00	0.00	3.00	0.00	6.00	0.00	11.83	0.00	24.25	0.00
6	C T	C	-0.25	0.00	0.50	0.00	1.00	0.00	2.00	0.00	3.00	0.00	6.00	0.00	12.45	0.00	27.00	0.00
7	T C	C	-0.03	0.00	0.50	0.00	1.05	0.00	2.05	0.00	3.05	0.00	6.00	0.00	11.80	0.00	23.97	0.00
8	C T	C	-0.07	0.00	0.50	0.00	1.08	0.00	2.08	0.00	3.12	0.00	6.17	0.00	11.83	0.00	23.78	0.00
9	T C	C	-0.08	0.00	0.45	0.00	0.92	0.00	2.00	0.00	2.92	0.00	6.00	0.00	12.00	0.00	23.93	0.00
10	C T	C	-24.00	0.00	0.50	0.00	1.00	0.00	2.00	0.00	3.00	0.00	6.08	0.00	11.92	0.00	23.92	0.00
11	C T	C	-0.02	0.00	0.75	0.00	1.12	0.00	2.12	0.00	3.25	0.00	6.17	0.00	12.00	0.00	24.83	0.00
12	C T	C	-0.17	0.00	0.53	0.00	1.08	0.00	2.05	0.00	3.05	0.00	5.97	0.00	11.97	0.00	23.92	0.00
13	T C	C	-0.08	0.00	0.58	0.00	1.00	0.00	2.17	0.00	3.17	0.00	6.08	0.00	12.17	0.00	24.25	0.00
14	T C	C	-0.08	0.00	0.58	0.00	1.05	0.00	2.02	0.00	3.08	0.00	6.13	0.00	11.92	0.00	24.00	0.00
15	C T	C	-0.05	0.00	0.45	0.00	0.88	0.00	2.17	0.00	3.33	0.00	6.13	0.00	12.07	0.00	24.08	0.00
16	C T	C	-0.08	0.00	0.57	0.00	1.05	0.00	2.05	0.00	3.00	0.00	6.00	0.00	11.97	0.00	24.13	0.00
17	T C	C	-0.20	0.00	0.50	0.00	1.63	0.00	2.38	0.00	3.13	0.00	5.90	0.00	11.63	0.00	23.47	0.00
18	T C	C	-0.08	0.00	0.50	0.00	1.02	0.00	2.00	0.00	3.00	0.00	6.02	0.00	11.92	0.00	26.42	0.00
19	C T	C	-0.03	0.00	0.50	0.00	0.95	0.00	1.97	0.00	3.00	0.00	6.12	0.00	11.58	0.00	26.13	0.00
20	T C	C	-0.02	0.00	0.50	0.00	1.05	0.00	2.10	0.00	3.02	0.00	6.07	0.00	11.73	0.00	23.82	0.00
21	C T	C	-0.05	0.00	0.55	0.00	1.00	0.00	2.00	0.00	3.02	0.00	6.03	0.00	11.67	0.00	23.95	0.00
22	C T	C	-0.03	0.00	0.50	0.00	1.00	0.00	2.00	0.00	3.00	0.00	6.00	0.00	11.47	0.00	23.97	0.00
23	C T	C	-0.03	0.00	0.50	0.00	1.02	0.00	2.00	0.00	3.12	0.00	6.13	0.00	11.72	0.00	24.00	0.00
Mean			-5.52	0.00	0.53	0.00	1.05	0.00	2.06	0.00	3.07	0.00	6.07	0.00	11.88	0.00	24.36	0.00
STD			20.84	0.00	0.07	0.00	0.14	0.00	0.09	0.00	0.09	0.00	0.09	0.00	0.23	0.00	0.92	0.00
CV					12.32		13.49		4.43		3.03		1.52		1.89		3.77	

Table A 9: Concentration of total sum of isoflavones for each subject given the capsule formulation.

snr	Seq.	Period	t. 0.0	M. 0.0	t. 0.5	M. 0.5	t. 1.0	M. 1.0	t. 2.0	M. 2.0	t. 3.0	M. 3.0	t. 6.0	M. 6.0	t. 12.0	M. 12.0	t. 24.0	M. 24.0
1	T C	C	-0.03	24.00	0.50	38.00	1.00	181.00	2.00	618.00	3.05	567.00	6.17	803.00	12.00	632.00	24.00	298.00
2	T C	C	-0.08	0.00	0.62	441.00	1.07	1587.00	2.07	2043.00	3.08	1670.00	6.32	1983.00	11.58	822.00	24.08	371.00
3	T C	C	-0.05	35.00	0.58	2070.00	1.08	1966.00	2.08	1406.00	3.08	1226.00	6.08	948.00	12.08	990.00	24.08	331.00
4	T C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	C T	C	-96.00	9.70	0.50	163.80	1.00	665.70	2.00	520.30	3.00	477.00	6.00	925.40	11.83	560.90	24.25	262.90
6	C T	C	-0.25	257.70	0.50	111.00	1.00	297.50	2.00	775.40	3.00	644.10	6.00	1525.60	12.45	1315.10	27.00	768.70
7	T C	C	-0.03	32.00	0.50	512.00	1.05	863.00	2.05	1306.00	3.05	1312.00	6.00	175.00	11.80	106.00	23.97	26.00
8	C T	C	-0.07	0.00	0.50	1442.20	1.08	1837.80	2.08	795.90	3.12	1577.50	6.17	248.10	11.83	270.80	23.78	89.20
9	T C	C	-0.08	0.00	0.45	163.00	0.92	156.00	2.00	360.00	2.92	259.00	6.00	209.00	12.00	169.00	23.93	66.00
10	C T	C	-24.00	9.20	0.50	1212.40	1.00	425.40	2.00	650.10	3.00	465.80	6.08	392.50	11.92	740.50	23.92	213.60
11	C T	C	-0.02	17.50	0.75	745.10	1.12	910.10	2.12	383.20	3.25	1514.90	6.17	548.40	12.00	449.90	24.83	140.80
12	C T	C	-0.17	81.50	0.53	95.80	1.08	160.60	2.05	1207.60	3.05	1219.70	5.97	891.20	11.97	468.10	23.92	457.70
13	T C	C	-0.08	17.00	0.58	1545.00	1.00	2118.00	2.17	907.00	3.17	688.00	6.08	916.00	12.17	589.00	24.25	323.00
14	T C	C	-0.08	66.00	0.58	1351.00	1.05	1267.00	2.02	1032.00	3.08	797.00	6.13	925.00	11.92	328.00	24.00	111.00
15	C T	C	-0.05	144.00	0.45	380.30	0.88	297.80	2.17	229.00	3.33	623.20	6.13	888.00	12.07	647.90	24.08	218.40
16	C T	C	-0.08	0.00	0.57	332.00	1.05	584.00	2.05	1855.00	3.00	979.00	6.00	981.00	11.97	520.00	24.13	338.00
17	T C	C	-0.20	45.00	0.50	205.00	1.63	776.00	2.38	708.00	3.13	799.00	5.90	1390.00	11.63	488.00	23.47	206.00
18	T C	C	-0.08	36.00	0.50	694.00	1.02	949.00	2.00	1771.00	3.00	2173.00	6.02	1099.00	11.92	782.00	26.42	163.00
19	C T	C	-0.03	16.00	0.50	67.00	0.95	644.00	1.97	867.00	3.00	613.00	6.12	1158.00	11.58	478.00	26.13	183.00
20	T C	C	-0.02	0.00	0.50	104.00	1.05	293.00	2.10	357.00	3.02	249.00	6.07	316.00	11.73	167.00	23.82	44.00
21	C T	C	-0.05	0.00	0.55	31.00	1.00	1814.00	2.00	2042.00	3.02	2150.00	6.03	1357.00	11.67	878.00	23.95	1867.00
22	C T	C	-0.03	23.00	0.50	145.00	1.00	352.00	2.00	2051.00	3.00	1768.00	6.00	2082.00	11.47	698.00	23.97	159.00
23	C T	C	-0.03	9.00	0.50	94.00	1.02	391.00	2.00	1935.00	3.12	989.00	6.13	1439.00	11.72	753.00	24.00	254.00
Mean			-5.52	37.39	0.53	542.85	1.05	842.54	2.06	1082.70	3.07	1034.60	6.07	963.65	11.88	584.24	24.36	313.24
STD			20.84	59.83	0.07	596.69	0.14	640.10	0.09	622.21	0.09	575.84	0.09	529.52	0.23	288.58	0.92	383.21
CV				160.01	12.32	109.92	13.49	75.97	4.43	57.47	3.03	55.66	1.52	54.95	1.89	49.39	3.77	122.34

Table A 10: Residual concentration of daidzein for each subject given the tablet formulation.

snr	Seq.	Period	Tp. 1	Day 1	Tp. 4	Day 4	Tp. 8	Day 8	Tp. 15	Day 15	Tp. 29	Day 29
5	C T	T	1.00	81.00	4.00	103.00	8.00	168.00	15.00	96.00	29.00	750.00
6	C T	T	1.00	41.00	4.00	17.00	8.00	43.00	15.00	255.00	30.00	17.00
8	C T	T	1.00	0.00	4.00	7.00	8.00	19.00	15.00	497.00	29.00	479.00
10	C T	T	1.00	45.00	3.00	208.00	8.00	116.00	15.00	146.00	25.00	67.00
11	C T	T	1.00	14.00	4.00	79.00	8.00	114.00	15.00	105.00	29.00	364.00
12	C T	T	1.00	24.00	4.00	220.00	8.00	83.00	15.00	156.00	31.00	50.00
15	C T	T	1.00	19.00	4.00	72.00	8.00	14.00	15.00	24.00	29.00	26.00
16	C T	T	.	.	.	.	.	.	.	.	.	.
19	C T	T	1.00	35.00	5.00	30.40	8.00	27.90	15.00	213.20	29.00	4.60
21	C T	T	1.00	0.00	4.00	7.00	8.00	3.00	15.00	15.00	29.00	10.00
22	C T	T	1.00	4.00	4.00	33.00	8.00	42.00	15.00	38.00	29.00	21.00
23	C T	T	.	.	.	.	.	.	.	.	.	.
Mean			1.00	26.30	4.00	77.64	8.00	62.99	15.00	154.52	28.90	178.86
STD			0.00	25.22	0.47	78.75	0.00	54.61	0.00	144.09	1.52	260.99
CV			0.00	95.89	11.79	101.43	0.00	86.70	0.00	93.25	5.27	145.92

Table A 11: Residual concentration of genistein for each subject given the tablet formulation.

snr	Seq.	Period	Tp. 1	Day 1	Tp. 4	Day 4	Tp. 8	Day 8	Tp. 15	Day 15	Tp. 29	Day 29
5	C T	T	1.00	475.00	4.00	1358.00	8.00	1475.00	15.00	653.00	29.00	970.00
6	C T	T	1.00	654.00	4.00	298.00	8.00	535.00	15.00	1657.00	30.00	386.00
8	C T	T	1.00	23.00	4.00	267.00	8.00	514.00	15.00	169.00	29.00	861.00
10	C T	T	1.00	156.00	3.00	756.00	8.00	316.00	15.00	390.00	25.00	460.00
11	C T	T	1.00	29.00	4.00	355.00	8.00	446.00	15.00	281.00	29.00	907.00
12	C T	T	1.00	378.00	4.00	923.00	8.00	292.00	15.00	512.00	31.00	380.00
15	C T	T	1.00	182.00	4.00	539.00	8.00	290.00	15.00	233.00	29.00	333.00
16	C T	T	.	.	.	.	.	.	.	.	.	.
19	C T	T	1.00	153.00	5.00	373.00	8.00	370.00	15.00	600.00	29.00	222.00
21	C T	T	1.00	22.00	4.00	174.00	8.00	147.00	15.00	218.00	29.00	343.00
22	C T	T	1.00	32.00	4.00	188.00	8.00	191.00	15.00	199.00	29.00	139.00
23	C T	T	.	.	.	.	.	.	.	.	.	.
Mean			1.00	210.40	4.00	523.10	8.00	457.60	15.00	491.20	28.90	500.10
STD			0.00	220.43	0.47	381.91	0.00	379.36	0.00	445.03	1.52	299.26
CV			0.00	104.77	11.79	73.01	0.00	82.90	0.00	90.60	5.27	59.84

Table A 12: Residual concentration of equol for each subject given the tablet formulation.

snr	Seq.	Period	Tp. 1	Day 1	Tp. 4	Day 4	Tp. 8	Day 8	Tp. 15	Day 15	Tp. 29	Day 29
5	C T	T	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
6	C T	T	1.00	0	4.00	0.00	8.00	0.00	15.00	491.00	30.00	337.00
8	C T	T	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
10	C T	T	1.00	0	3.00	0.00	8.00	0.00	15.00	0.00	25.00	0.00
11	C T	T	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
12	C T	T	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	31.00	0.00
15	C T	T	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
16	C T	T	.	.	.	.	.	.	.	.	.	.
19	C T	T	1.00	0	5.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
21	C T	T	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
22	C T	T	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
23	C T	T	.	.	.	.	.	.	.	.	.	.
Mean			1.00		4.00	0.00	8.00	0.00	15.00	49.10	28.90	33.70
STD			0.00		0.47	0.00	0.00	0.00	0.00	155.27	1.52	106.57
CV			0.00		11.79		0.00		0.00	316.23	5.27	316.23

Table A 13: Residual concentration of total sum of isoflavones for each subject given the tablet formulation.

snr	Seq.	Period	Tp. 1	Day 1	Tp. 4	Day 4	Tp. 8	Day 8	Tp. 15	Day 15	Tp. 29	Day 29
5	C T	T	1.00	556.00	4.00	1461.00	8.00	1643.00	15.00	749.00	29.00	1720.00
6	C T	T	1.00	695.00	4.00	315.00	8.00	578.00	15.00	2403.00	30.00	740.00
8	C T	T	1.00	23.00	4.00	274.00	8.00	533.00	15.00	666.00	29.00	1340.00
10	C T	T	1.00	201.00	3.00	964.00	8.00	432.00	15.00	536.00	25.00	527.00
11	C T	T	1.00	43.00	4.00	434.00	8.00	560.00	15.00	386.00	29.00	1271.00
12	C T	T	1.00	402.00	4.00	1143.00	8.00	375.00	15.00	668.00	31.00	430.00
15	C T	T	1.00	201.00	4.00	611.00	8.00	304.00	15.00	257.00	29.00	359.00
16	C T	T	.	.	.	.	.	.	.	.	.	.
19	C T	T	1.00	188.00	5.00	403.40	8.00	397.90	15.00	813.20	29.00	226.60
21	C T	T	1.00	22.00	4.00	181.00	8.00	150.00	15.00	233.00	29.00	353.00
22	C T	T	1.00	36.00	4.00	221.00	8.00	233.00	15.00	237.00	29.00	160.00
23	C T	T	.	.	.	.	.	.	.	.	.	.
Mean			1.00	236.70	4.00	600.74	8.00	520.59	15.00	694.82	28.90	712.66
STD			0.00	238.93	0.47	439.91	0.00	418.44	0.00	638.71	1.52	540.71
CV			0.00	100.94	11.79	73.23	0.00	80.38	0.00	91.92	5.27	75.87

Table A 14: Residual concentration of daidzein for each subject given the capsule formulation.

snr	Seq.	Period	Tp. 1	Day 1	Tp. 4	Day 4	Tp. 8	Day 8	Tp. 15	Day 15	Tp. 29	Day 29
1	T C	C	1.00	12.00	4.00	24.00	8.00	12.00	15.00	15.00	29.00	18.00
2	T C	C	1.00	11.00	4.00	0.00	8.00	0.00	15.00	0.00	29.00	8.00
3	T C	C	1.00	47.00	4.00	884.00	8.00	57.00	15.00	52.00	29.00	21.00
4	T C	C	.	.	.	.	.	.	.	.	.	.
7	T C	C	1.00	0.00	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
9	T C	C	1.00	6.00	3.00	14.00	8.00	21.00	15.00	26.00	29.00	36.00
13	T C	C	1.00	9.00	4.00	94.00	8.00	62.00	15.00	99.00	25.00	10.00
14	T C	C	1.00	9.00	4.00	15.00	7.00	13.00	14.00	17.00	29.00	382.00
17	T C	C	1.00	7.00	3.00	0.00	8.00	158.00	15.00	278.00	21.00	0.00
18	T C	C	1.00	9.00	5.00	138.00	8.00	209.00	15.00	30.00	29.00	47.00
20	T C	C	1.00	6.00	4.00	7.20	8.00	2.80	15.00	14.70	29.00	9.80
Mean			1.00	11.60	3.90	117.62	7.90	53.48	14.90	53.17	27.80	53.18
STD			0.00	12.88	0.57	273.26	0.32	72.95	0.32	84.21	2.70	116.51
CV			0.00	111.01	14.56	232.32	4.00	136.41	2.12	158.38	9.71	219.09

Table A 15: Residual concentration of genistein for each subject given the capsule formulation.

snr	Seq.	Period	Tp. 1	Day 1	Tp. 4	Day 4	Tp. 8	Day 8	Tp. 15	Day 15	Tp. 29	Day 29
1	T C	C	1.00	286.00	4.00	342.00	8.00	136.00	15.00	346.00	29.00	213.00
2	T C	C	1.00	360.00	4.00	137.00	8.00	125.00	15.00	148.00	29.00	331.00
3	T C	C	1.00	284.00	4.00	1704.00	8.00	344.00	15.00	288.00	29.00	254.00
4	T C	C	.	.	.	.	.	.	.	.	.	.
7	T C	C	1.00	26.00	4.00	68.00	8.00	107.00	15.00	224.00	29.00	55.00
9	T C	C	1.00	60.00	3.00	326.00	8.00	370.00	15.00	355.00	29.00	86.00
13	T C	C	1.00	314.00	4.00	531.00	8.00	220.00	15.00	313.00	25.00	304.00
14	T C	C	1.00	102.00	4.00	171.00	7.00	200.00	14.00	233.00	29.00	1292.00
17	T C	C	1.00	199.00	3.00	94.00	8.00	1246.00	15.00	1020.00	21.00	104.00
18	T C	C	1.00	154.00	5.00	999.00	8.00	1366.00	15.00	519.00	29.00	744.00
20	T C	C	1.00	38.00	4.00	173.70	8.00	147.10	15.00	217.50	29.00	342.60
Mean			1.00	182.30	3.90	454.57	7.90	426.11	14.90	366.35	27.80	372.56
STD			0.00	123.72	0.57	519.84	0.32	473.01	0.32	251.21	2.70	377.90
CV			0.00	67.87	14.56	114.36	4.00	111.01	2.12	68.57	9.71	101.43

Table A 16: Residual concentration of equol for each subject given the capsule formulation.

snr	Seq.	Period	Tp. 1	Day 1	Tp. 4	Day 4	Tp. 8	Day 8	Tp. 15	Day 15	Tp. 29	Day 29
1	T C	C	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
2	T C	C	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
3	T C	C	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
4	T C	C	.	.	.	.	.	.	.	.	.	.
7	T C	C	1.00	0	4.00	296.00	8.00	156.00	15.00	159.00	29.00	0.00
9	T C	C	1.00	0	3.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
13	T C	C	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	25.00	0.00
14	T C	C	1.00	0	4.00	0.00	7.00	0.00	14.00	0.00	29.00	0.00
17	T C	C	1.00	0	3.00	0.00	8.00	0.00	15.00	0.00	21.00	0.00
18	T C	C	1.00	0	5.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
20	T C	C	1.00	0	4.00	0.00	8.00	0.00	15.00	0.00	29.00	0.00
Mean			1.00		3.90	29.60	7.90	15.60	14.90	15.90	27.80	0.00
STD			0.00		0.57	93.60	0.32	49.33	0.32	50.28	2.70	0.00
CV			0.00		14.56	316.23	4.00	316.23	2.12	316.23	9.71	

Table A 17: Residual concentration of total sum of isoflavones for each subject given the capsule formulation.

snr	Seq.	Period	Tp. 1	Day 1	Tp. 4	Day 4	Tp. 8	Day 8	Tp. 15	Day 15	Tp. 29	Day 29
1	T C	C	1.00	298.00	4.00	366.00	8.00	148.00	15.00	361.00	29.00	231.00
2	T C	C	1.00	371.00	4.00	137.00	8.00	125.00	15.00	148.00	29.00	339.00
3	T C	C	1.00	331.00	4.00	2588.00	8.00	401.00	15.00	340.00	29.00	275.00
4	T C	C	.	.	.	.	.	.	.	.	.	.
7	T C	C	1.00	26.00	4.00	364.00	8.00	263.00	15.00	383.00	29.00	55.00
9	T C	C	1.00	66.00	3.00	340.00	8.00	391.00	15.00	381.00	29.00	122.00
13	T C	C	1.00	323.00	4.00	625.00	8.00	282.00	15.00	412.00	25.00	314.00
14	T C	C	1.00	111.00	4.00	186.00	7.00	213.00	14.00	250.00	29.00	1674.00
17	T C	C	1.00	206.00	3.00	94.00	8.00	1404.00	15.00	1298.00	21.00	104.00
18	T C	C	1.00	163.00	5.00	1137.00	8.00	1575.00	15.00	549.00	29.00	791.00
20	T C	C	1.00	44.00	4.00	180.90	8.00	149.90	15.00	232.20	29.00	352.40
Mean			1.00	193.90	3.90	601.79	7.90	495.19	14.90	435.42	27.80	425.74
STD			0.00	130.24	0.57	762.79	0.32	534.11	0.32	322.51	2.70	484.29
CV			0.00	67.17	14.56	126.75	4.00	107.86	2.12	74.07	9.71	113.75

Table A 18: Summary of parameters for daidzein for each subject given the tablet formulation.

snr	Seq.	Period	$AUC_{0\rightarrow 24}$	$c\_max_{0\rightarrow 24}$	$t\_max_{0\rightarrow 24}$
1	T C	T	.	.	.
2	T C	T	59.10	125.10	6.00
3	T C	T	75.23	151.30	11.92
4	T C	T	.	.	.
5	C T	T	141.21	229.00	11.50
6	C T	T	62.92	118.00	14.00
7	T C	T	102.96	264.50	5.52
8	C T	T	17.52	47.00	6.08
9	T C	T	158.55	343.20	6.08
10	C T	T	13.54	41.82	24.00
11	C T	T	36.68	70.00	11.62
12	C T	T	61.59	87.00	5.65
13	T C	T	99.72	278.20	6.33
14	T C	T	126.24	216.50	11.72
15	C T	T	64.68	228.00	3.32
16	C T	T	.	.	.
17	T C	T	75.31	130.00	11.92
18	T C	T	186.06	377.00	1.00
19	C T	T	137.69	253.00	6.07
20	T C	T	235.95	538.00	6.17
21	C T	T	18.05	61.00	2.00
22	C T	T	29.21	66.00	6.05
23	C T	T	.	.	.
Mean/Median*			89.59	190.77	6.08
STD			61.50	132.17	5.29
CV			68.65	69.28	

Table A 19: Summary of parameters for genistein for each subject given the tablet formulation.

snr	Seq.	Period	$AUC_{0\rightarrow 24}$	$c\_max_{0\rightarrow 24}$	$t\_max_{0\rightarrow 24}$
1	T C	T	.	.	.
2	T C	T	175.05	248.80	6.00
3	T C	T	240.63	1526.60	3.00
4	T C	T	.	.	.
5	C T	T	552.39	773.00	11.50
6	C T	T	423.28	653.67	24.00
7	T C	T	283.57	611.90	5.52
8	C T	T	58.03	105.00	6.08
9	T C	T	418.76	617.20	6.08
10	C T	T	49.96	145.49	24.00
11	C T	T	60.09	86.00	6.08
12	C T	T	437.15	572.00	5.65
13	T C	T	272.95	422.70	6.33
14	T C	T	144.10	221.80	11.72
15	C T	T	269.90	566.00	3.32
16	C T	T	.	.	.
17	T C	T	272.05	503.00	2.08
18	T C	T	776.51	1381.00	11.68
19	C T	T	330.13	514.00	6.07
20	T C	T	524.64	1190.00	3.08
21	C T	T	98.46	215.00	6.05
22	C T	T	67.29	149.00	6.05
23	C T	T	.	.	.
Mean/Median*			287.10	552.74	6.07
STD			198.13	421.07	6.23
CV			69.01	76.18	

Table A 20: Summary of parameters for sum of all isoflavones for each subject given the tablet formulation.

snr	Seq.	Period	$AUC_{0\rightarrow 24}$	$c\_max_{0\rightarrow 24}$	$t\_max_{0\rightarrow 24}$
1	T C	T	.	.	.
2	T C	T	234.15	373.90	6.00
3	T C	T	315.87	1576.70	3.00
4	T C	T	.	.	.
5	C T	T	693.60	1002.00	11.50
6	C T	T	486.20	730.00	14.00
7	T C	T	386.53	876.40	5.52
8	C T	T	75.55	152.00	6.08
9	T C	T	577.31	960.40	6.08
10	C T	T	63.49	187.31	24.00
11	C T	T	96.77	153.00	11.62
12	C T	T	498.73	659.00	5.65
13	T C	T	372.67	700.90	6.33
14	T C	T	270.34	438.30	11.72
15	C T	T	334.58	794.00	3.32
16	C T	T	.	.	.
17	T C	T	347.36	601.00	2.08
18	T C	T	962.57	1700.00	11.68
19	C T	T	467.82	767.00	6.07
20	T C	T	760.59	1472.00	3.08
21	C T	T	116.51	275.00	2.00
22	C T	T	96.50	215.00	6.05
23	C T	T	.	.	.
Mean/Median*			376.69	717.57	6.07
STD			249.21	473.03	5.37
CV			66.16	65.92	

Table A 21: Summary of parameters for daidzein for each subject given the capsule formulation.

snr	Seq.	Period	$AUC_{0\rightarrow 24}$	$c\_max_{0\rightarrow 24}$	$t\_max_{0\rightarrow 24}$
1	T C	C	91.79	201.00	6.17
2	T C	C	184.07	529.00	1.07
3	T C	C	197.42	737.00	0.58
4	T C	C	.	.	.
5	C T	C	93.24	206.30	6.00
6	C T	C	135.20	255.90	6.00
7	T C	C	60.29	314.00	3.05
8	C T	C	147.40	1074.10	3.12
9	T C	C	43.86	275.00	2.00
10	C T	C	138.84	292.70	0.50
11	C T	C	153.23	510.20	3.25
12	C T	C	90.79	330.20	2.05
13	T C	C	129.00	684.00	1.00
14	T C	C	104.03	382.00	0.58
15	C T	C	115.26	260.50	6.13
16	C T	C	135.74	521.00	2.05
17	T C	C	128.30	373.00	5.90
18	T C	C	166.74	786.00	1.02
19	C T	C	137.63	378.00	6.12
20	T C	C	43.66	119.00	6.07
21	C T	C	184.26	742.00	1.00
22	C T	C	219.69	641.00	6.00
23	C T	C	147.79	554.00	2.00
Mean/Median*			129.47	462.09	2.55
STD			46.87	238.27	2.29
CV			36.20	51.56	

Table A 22: Summary of parameters for genistein for each subject given the capsule formulation.

snr	Seq.	Period	$AUC_{0\rightarrow 24}$	$c\_max_{0\rightarrow 24}$	$t\_max_{0\rightarrow 24}$
1	T C	C	449.56	602.00	6.17
2	T C	C	858.43	1575.00	2.07
3	T C	C	704.35	1398.00	1.08
4	T C	C	.	.	.
5	C T	C	442.85	719.10	6.00
6	C T	C	970.16	1269.70	6.00
7	T C	C	219.99	1038.00	2.05
8	C T	C	283.15	1391.10	1.08
9	T C	C	120.38	195.00	2.92
10	C T	C	381.03	919.70	0.50
11	C T	C	342.81	1004.70	3.25
12	C T	C	522.70	984.50	3.05
13	T C	C	545.44	1434.00	1.00
14	T C	C	398.50	984.00	1.05
15	C T	C	424.95	627.50	6.13
16	C T	C	509.46	1334.00	2.05
17	T C	C	470.71	1017.00	5.90
18	T C	C	698.21	1694.00	3.00
19	C T	C	417.21	780.00	6.12
20	T C	C	134.17	292.00	2.10
21	C T	C	1191.62	1871.40	24.00
22	C T	C	697.74	1509.00	2.00
23	C T	C	639.45	1381.00	2.00
Mean/Median*			519.22	1091.85	2.51
STD			261.29	439.52	4.87
CV			50.32	40.25	

Table A 23 : Summary of parameters for sum of all isoflavones for each subject given the capsule formulation.

snr	Seq.	Period	$AUC_{0\rightarrow 24}$	$c\_max_{0\rightarrow 24}$	$t\_max_{0\rightarrow 24}$
1	T C	C	541.35	803.00	6.17
2	T C	C	1042.51	2043.00	2.07
3	T C	C	901.78	2070.00	0.58
4	T C	C	.	.	.
5	C T	C	536.09	925.40	6.00
6	C T	C	1105.36	1525.60	6.00
7	T C	C	280.28	1312.00	3.05
8	C T	C	430.41	1837.80	1.08
9	T C	C	164.24	360.00	2.00
10	C T	C	519.87	1212.40	0.50
11	C T	C	496.04	1514.90	3.25
12	C T	C	613.49	1219.70	3.05
13	T C	C	674.44	2118.00	1.00
14	T C	C	502.53	1351.00	0.58
15	C T	C	540.21	888.00	6.13
16	C T	C	645.20	1855.00	2.05
17	T C	C	599.02	1390.00	5.90
18	T C	C	864.94	2173.00	3.00
19	C T	C	554.85	1158.00	6.12
20	T C	C	177.83	357.00	2.10
21	C T	C	1375.78	2150.00	3.02
22	C T	C	917.43	2082.00	6.00
23	C T	C	787.25	1935.00	2.00
Mean/Median*			648.68	1467.31	3.01
STD			296.39	567.66	2.11
CV			45.69	38.69	

Table A 24: Residual concentration: Summary of parameters for daidzein for each subject given the tablet formulation in period II.

snr	Seq.	Period	AUC_{res}	c_max_{res}	t_max_{res}
5	C T	T	7664.00	750.00	29.00
6	C T	T	3265.07	255.00	15.00
8	C T	T	8700.50	497.00	15.00
10	C T	T	3249.80	208.00	3.00
11	C T	T	4575.00	364.00	29.00
12	C T	T	3343.25	220.00	4.00
15	C T	T	791.50	72.00	4.00
16	C T	T	.	.	.
19	C T	T	2586.70	213.20	15.00
21	C T	T	268.50	15.00	15.00
22	C T	T	898.50	42.00	8.00
23	C T	T	.	.	.
Mean/Median*			3534.28	263.62	15.00
STD			2809.72	225.18	9.49
CV			79.50	85.42	

Table A 25: Residual concentration: Summary of parameters for genistein for each subject given the tablet formulation in period II.

snr	Seq.	Period	AUC_{res}	c_max_{res}	t_max_{res}
5	C T	T	27224.5	1475.00	8.00
6	C T	T	25660.1	1657.00	15.00
8	C T	T	11597.5	861.00	29.00
10	C T	T	12209.0	756.00	3.00
11	C T	T	13038.5	907.00	29.00
12	C T	T	13555.0	923.00	4.00
15	C T	T	8532.00	539.00	4.00
16	C T	T	.	.	.
19	C T	T	11315.5	600.00	15.00
21	C T	T	6140.50	343.00	29.00
22	C T	T	4819.00	199.00	15.00
23	C T	T	.	.	.
Mean/Median*			13409.2	826.00	15.00
STD			7458.22	458.71	10.66
CV			55.62	55.53	

Table A 26: Residual concentration: Summary of parameters for equol for each subject given the tablet formulation in period II.

snr	Seq.	Period	AUC_{res}	c_max_{res}	t_max_{res}
5	C T	T	0.00	0.00	29.00
6	C T	T	7586.37	491.00	15.00
8	C T	T	0.00	0.00	29.00
10	C T	T	0.00	0.00	29.00
11	C T	T	0.00	0.00	29.00
12	C T	T	0.00	0.00	29.00
15	C T	T	0.00	0.00	29.00
16	C T	T	.	.	.
19	C T	T	0.00	0.00	29.00
21	C T	T	0.00	0.00	29.00
22	C T	T	0.00	0.00	29.00
23	C T	T	.	.	.
Mean/Median*			758.64	49.10	29.00
STD			2399.02	155.27	4.43
CV			316.23	316.23	

Table A 27: Residual concentration: Summary of parameters for sum of all isoflavones for each subject given the tablet formulation in period II.

snr	Seq.	Period	AUC_{res}	c_max_{res}	t_max_{res}
5	C T	T	34888.5	1720.00	29.00
6	C T	T	36511.6	2403.00	15.00
8	C T	T	20298.0	1340.00	29.00
10	C T	T	15458.8	964.00	3.00
11	C T	T	17613.5	1271.00	29.00
12	C T	T	16898.3	1143.00	4.00
15	C T	T	9323.50	611.00	4.00
16	C T	T	.	.	.
19	C T	T	13902.2	813.20	15.00
21	C T	T	6409.00	353.00	29.00
22	C T	T	5717.50	237.00	15.00
23	C T	T	.	.	.
Mean/Median*			17702.1	1085.52	15.00
STD			10632.2	650.76	11.16
CV			60.06	59.95	

Table A 28: Residual concentration: Summary of parameters for daidzein for each subject given the capsule formulation in period II.

snr	Seq.	Period	AUC_{res}	c_max_{res}	t_max_{res}
1	T C	C	451.50	24.00	4.00
2	T C	C	72.50	11.00	1.00
3	T C	C	4171.00	884.00	4.00
4	T C	C	.	.	.
7	T C	C	0.00	0.00	29.00
9	T C	C	706.00	36.00	29.00
13	T C	C	1723.00	99.00	15.00
14	T C	C	3175.50	382.00	29.00
17	T C	C	3874.00	278.00	15.00
18	T C	C	2190.00	209.00	8.00
20	T C	C	272.55	14.70	15.00
Mean/Median*			1663.61	193.77	15.00
STD			1611.06	275.86	10.93
CV			96.84	142.36	

Table A 29: Residual concentration: Summary of parameters for genistein for each subject given the capsule formulation in period II.

snr	Seq.	Period	AUC_{res}	c_max_{res}	t_max_{res}
1	T C	C	7498.00	346.00	15.00
2	T C	C	5578.00	360.00	1.00
3	T C	C	13084.0	1704.00	4.00
4	T C	C	.	.	.
7	T C	C	3602.50	224.00	15.00
9	T C	C	7750.50	370.00	8.00
13	T C	C	8928.80	531.00	4.00
14	T C	C	13919.0	1292.00	29.00
17	T C	C	18714.0	1246.00	8.00
18	T C	C	21292.0	1366.00	8.00
20	T C	C	6155.95	342.60	29.00
Mean/Median*			10652.3	778.16	8.00
STD			5885.81	554.95	9.96
CV			55.25	71.32	

Table A 30: Residual concentration: Summary of parameters for equol for each subject given the capsule formulation in period II.

snr	Seq.	Period	AUC_{res}	c_max_{res}	t_max_{res}
1	T C	C	0.00	0.00	29.00
2	T C	C	0.00	0.00	29.00
3	T C	C	0.00	0.00	29.00
4	T C	C	.	.	.
7	T C	C	3563.50	296.00	4.00
9	T C	C	0.00	0.00	29.00
13	T C	C	0.00	0.00	29.00
14	T C	C	0.00	0.00	29.00
17	T C	C	0.00	0.00	29.00
18	T C	C	0.00	0.00	29.00
20	T C	C	0.00	0.00	29.00
Mean/Median*			356.35	29.60	29.00
STD			1126.88	93.60	7.91
CV			316.23	316.23	

Table A 31: Residual concentration: Summary of parameters for sum of all isoflavones for each subject given the capsule formulation in period II.

snr	Seq.	Period	AUC_{res}	c_max_{res}	t_max_{res}
1	T C	C	7949.50	366.00	4.00
2	T C	C	5650.50	371.00	1.00
3	T C	C	17255.0	2588.00	4.00
4	T C	C	.	.	.
7	T C	C	7166.00	383.00	15.00
9	T C	C	8456.50	391.00	8.00
13	T C	C	10472.6	625.00	4.00
14	T C	C	17094.5	1674.00	29.00
17	T C	C	22588.0	1404.00	8.00
18	T C	C	23482.0	1575.00	8.00
20	T C	C	6428.50	352.40	29.00
Mean/Median*			12654.3	972.94	8.00
STD			6825.21	786.82	10.21
CV			53.94	80.87	

Table A 32: Daidzein: ln($AUC_{0\rightarrow 24}$) ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	1.064440	1.064440	5.76	0.0282
Error: MS(snr(arm))	17	3.143163	0.184892		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	3.143163	0.184892	0.38	0.9743
period	1	3.739516	3.739516	7.62	0.0134
treatment	1	2.622260	2.622260	5.34	0.0336
Error: MS(Error)	17	8.347994	0.491058		

Table A 33: Daidzein: ln($c\_max_{0\rightarrow 24}$) ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	1.931054	1.931054	12.65	0.0024
Error: MS(snr(arm))	17	2.594417	0.152613		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	2.594417	0.152613	0.29	0.9931
period	1	1.971580	1.971580	3.70	0.0712
treatment	1	9.115874	9.115874	17.13	0.0007
Error: MS(Error)	17	9.046514	0.532148		

Table A 34: Daidzein: $t\_max_{0\rightarrow 24}$ ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	25.418312	25.418312	1.65	0.2163
Error: MS(snr(arm))	17	262.013120	15.412536		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	262.013120	15.412536	0.83	0.6475
period	1	0.002325	0.002325	0.00	0.9912
treatment	1	239.470409	239.470409	12.89	0.0023
Error: MS(Error)	17	315.734180	18.572599		

Table A 35: Genistein: ln($AUC_{0\rightarrow 24}$) ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	0.272544	0.272544	0.55	0.4674
Error: MS(snr(arm))	17	8.383963	0.493174		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	8.383963	0.493174	0.97	0.5273
period	1	2.136247	2.136247	4.19	0.0565
treatment	1	4.532384	4.532384	8.89	0.0084
Error: MS(Error)	17	8.671720	0.510101		

Table A 36: Genistein: ln(c_$max_{0\rightarrow 24}$) ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	0.798291	0.798291	2.21	0.1552
Error: MS(snr(arm))	17	6.132101	0.360712		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	6.132101	0.360712	0.61	0.8418
period	1	2.048199	2.048199	3.46	0.0803
treatment	1	6.637247	6.637247	11.21	0.0038
Error: MS(Error)	17	10.066223	0.592131		

Table A 37: Genistein: t_$max_{0\rightarrow 24}$ ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	121.935349	121.935349	4.86	0.0416
Error: MS(snr(arm))	17	426.712983	25.100764		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	426.712983	25.100764	0.67	0.7899
period	1	0.152400	0.152400	0.00	0.9498
treatment	1	147.078127	147.078127	3.94	0.0637
Error: MS(Error)	17	635.402405	37.376612		

Table A 38: Sum of all isoflavones: ln($AUC_{0\rightarrow 24}$) ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	0.380887	0.380887	1.00	0.3303
Error: MS(snr(arm))	17	6.445345	0.379138		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	6.445345	0.379138	0.76	0.7066
period	1	2.525978	2.525978	5.10	0.0374
treatment	1	3.946889	3.946889	7.96	0.0117
Error: MS(Error)	17	8.425606	0.495624		

Table A 39: Sum of all isoflavones: ln($c\_max_{0\rightarrow 24}$) ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	1.027736	1.027736	4.15	0.0576
Error: MS(snr(arm))	17	4.213558	0.247856		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	4.213558	0.247856	0.49	0.9254
period	1	1.969684	1.969684	3.88	0.0654
treatment	1	6.396471	6.396471	12.60	0.0025
Error: MS(Error)	17	8.633551	0.507856		

Table A 40: Sum of all isoflavones: $t\_max_{0\rightarrow 24}$ ANOVA results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
arm	1	52.878967	52.878967	4.23	0.0554
Error: MS(snr(arm))	17	212.517064	12.501004		

Source	DF	Type III SS	Mean Square	F Value	Pr > F
snr(arm)	17	212.517064	12.501004	0.64	0.8178
period	1	2.376850	2.376850	0.12	0.7318
treatment	1	184.505207	184.505207	9.43	0.0069
Error: MS(Error)	17	332.743698	19.573159		

Table A 41: Period sums, period differences, and cross-over differences for log($AUC_{0\rightarrow 24}$) for daidzein.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	4.52	.	.	.
2	T C	4.08	5.22	9.29	1.14	1.14
3	T C	4.32	5.29	9.61	0.96	0.96
4	T C	.	.	.	.	.
5	C T	4.54	4.95	9.49	0.42	-0.42
6	C T	4.91	4.14	9.05	-0.76	0.76
7	T C	4.63	4.10	8.73	-0.54	-0.54
8	C T	4.99	2.86	7.86	-2.13	2.13
9	T C	5.07	3.78	8.85	-1.29	-1.29
10	C T	4.93	2.61	7.54	-2.33	2.33
11	C T	5.03	3.60	8.63	-1.43	1.43
12	C T	4.51	4.12	8.63	-0.39	0.39
13	T C	4.60	4.86	9.46	0.26	0.26
14	T C	4.84	4.64	9.48	-0.19	-0.19
15	C T	4.75	4.17	8.92	-0.58	0.58
16	C T	4.91	.	.	.	.
17	T C	4.32	4.85	9.18	0.53	0.53
18	T C	5.23	5.12	10.34	-0.11	-0.11
19	C T	4.92	4.93	9.85	0.00	-0.00
20	T C	5.46	3.78	9.24	-1.69	-1.69
21	C T	5.22	2.89	8.11	-2.32	2.32
22	C T	5.39	3.37	8.77	-2.02	2.02
23	C T	5.00	.	.	.	.
Mean/Median*		4.84	4.19	9.00	-0.66	0.56
STD		0.36	0.82	0.68	1.10	1.16
CV		7.41	19.55	7.60		

Table A 42: Period sums, period differences, and cross-over differences for log($c\_max_{0\rightarrow 24}$) for daidzein.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	5.30	.	.	.
2	T C	4.83	6.27	11.10	1.44	1.44
3	T C	5.02	6.60	11.62	1.58	1.58
4	T C	.	.	.	.	.
5	C T	5.33	5.43	10.76	0.10	-0.10
6	C T	5.54	4.77	10.32	-0.77	0.77
7	T C	5.58	5.75	11.33	0.17	0.17
8	C T	6.98	3.85	10.83	-3.13	3.13
9	T C	5.84	5.62	11.46	-0.22	-0.22
10	C T	5.68	3.73	9.41	-1.95	1.95
11	C T	6.23	4.25	10.48	-1.99	1.99
12	C T	5.80	4.47	10.27	-1.33	1.33
13	T C	5.63	6.53	12.16	0.90	0.90
14	T C	5.38	5.95	11.32	0.57	0.57
15	C T	5.56	5.43	10.99	-0.13	0.13
16	C T	6.26	.	.	.	.
17	T C	4.87	5.92	10.79	1.05	1.05
18	T C	5.93	6.67	12.60	0.73	0.73
19	C T	5.93	5.53	11.47	-0.40	0.40
20	T C	6.29	4.78	11.07	-1.51	-1.51
21	C T	6.61	4.11	10.72	-2.50	2.50
22	C T	6.46	4.19	10.65	-2.27	2.27
23	C T	6.32	.	.	.	.
Mean/Median*		5.81	5.26	11.02	-0.51	1.00
STD		0.57	0.94	0.71	1.42	1.11
CV		9.78	17.85	6.44		

Table A 43: Period sums, period differences, and cross-over differences for $t\_max_{0\rightarrow 24}$ for daidzein.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	6.17	.	.	.
2	T C	6.00	1.07	7.07	-4.93	-4.93
3	T C	11.92	0.58	12.50	-11.34	-11.34
4	T C	.	.	.	.	.
5	C T	6.00	11.50	17.50	5.50	-5.50
6	C T	6.00	14.00	20.00	8.00	-8.00
7	T C	5.52	3.05	8.57	-2.47	-2.47
8	C T	3.12	6.08	9.20	2.96	-2.96
9	T C	6.08	2.00	8.08	-4.08	-4.08
10	C T	0.50	24.00	24.50	23.50	-23.50
11	C T	3.25	11.62	14.87	8.37	-8.37
12	C T	2.05	5.65	7.70	3.60	-3.60
13	T C	6.33	1.00	7.33	-5.33	-5.33
14	T C	11.72	0.58	12.30	-11.14	-11.14
15	C T	6.13	3.32	9.45	-2.81	2.81
16	C T	2.05	.	.	.	.
17	T C	11.92	5.90	17.82	-6.02	-6.02
18	T C	1.00	1.02	2.02	0.02	0.02
19	C T	6.12	6.07	12.19	-0.05	0.05
20	T C	6.17	6.07	12.24	-0.10	-0.10
21	C T	1.00	2.00	3.00	1.00	-1.00
22	C T	6.00	6.05	12.05	0.05	-0.05
23	C T	2.00	.	.	.	.
Mean/Median*		6.00	5.78	12.05	-0.05	-4.08
STD		3.43	5.76	5.65	7.85	5.92

Table A 44: Period sums, period differences, and cross-over differences for $\log(AUC_{0\rightarrow 24})$ for genistein.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	6.11	.	.	.
2	T C	5.17	6.76	11.92	1.59	1.59
3	T C	5.48	6.56	12.04	1.07	1.07
4	T C	.	.	.	.	.
5	C T	6.09	6.31	12.41	0.22	-0.22
6	C T	6.88	6.05	12.93	-0.83	0.83
7	T C	5.65	5.39	11.04	-0.25	-0.25
8	C T	5.65	4.06	9.71	-1.58	1.58
9	T C	6.04	4.79	10.83	-1.25	-1.25
10	C T	5.94	3.91	9.85	-2.03	2.03
11	C T	5.84	4.10	9.93	-1.74	1.74
12	C T	6.26	6.08	12.34	-0.18	0.18
13	T C	5.61	6.30	11.91	0.69	0.69
14	T C	4.97	5.99	10.96	1.02	1.02
15	C T	6.05	5.60	11.65	-0.45	0.45
16	C T	6.23	.	.	.	.
17	T C	5.61	6.15	11.76	0.55	0.55
18	T C	6.65	6.55	13.20	-0.11	-0.11
19	C T	6.03	5.80	11.83	-0.23	0.23
20	T C	6.26	4.90	11.16	-1.36	-1.36
21	C T	7.08	4.59	11.67	-2.49	2.49
22	C T	6.55	4.21	10.76	-2.34	2.34
23	C T	6.46	.	.	.	.
Mean/Median*		6.02	5.51	11.47	-0.51	0.72
STD		0.53	0.94	0.98	1.21	1.10
CV		8.85	17.07	8.55		

Table A 45: Period sums, period differences, and cross-over differences for log(c_max$_{0\rightarrow 24}$) for genistein.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	6.40	.	.	.
2	T C	5.52	7.36	12.88	1.85	1.85
3	T C	7.33	7.24	14.57	-0.09	-0.09
4	T C	.	.	.	.	.
5	C T	6.58	6.65	13.23	0.07	-0.07
6	C T	7.15	6.48	13.63	-0.66	0.66
7	T C	6.42	6.95	13.36	0.53	0.53
8	C T	7.24	4.65	11.89	-2.58	2.58
9	T C	6.43	5.27	11.70	-1.15	-1.15
10	C T	6.82	4.98	11.80	-1.84	1.84
11	C T	6.91	4.45	11.37	-2.46	2.46
12	C T	6.89	6.35	13.24	-0.54	0.54
13	T C	6.05	7.27	13.31	1.22	1.22
14	T C	5.40	6.89	12.29	1.49	1.49
15	C T	6.44	6.34	12.78	-0.10	0.10
16	C T	7.20	.	.	.	.
17	T C	6.22	6.92	13.15	0.70	0.70
18	T C	7.23	7.43	14.67	0.20	0.20
19	C T	6.66	6.24	12.90	-0.42	0.42
20	T C	7.08	5.68	12.76	-1.40	-1.40
21	C T	7.53	5.37	12.91	-2.16	2.16
22	C T	7.32	5.00	12.32	-2.32	2.32
23	C T	7.23	.	.	.	.
Mean/Median*		6.74	6.20	12.88	-0.51	0.86
STD		0.59	0.95	0.88	1.36	1.16
CV		8.74	15.36	6.81		

Table A 46: Period sums, period differences, and cross-over differences for t_max$_{0\rightarrow 24}$ for genistein.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	6.17	.	.	.
2	T C	6.00	2.07	8.07	-3.93	-3.93
3	T C	3.00	1.08	4.08	-1.92	-1.92
4	T C	.	.	.	.	.
5	C T	6.00	11.50	17.50	5.50	-5.50
6	C T	6.00	24.00	30.00	18.00	-18.00
7	T C	5.52	2.05	7.57	-3.47	-3.47
8	C T	1.08	6.08	7.16	5.00	-5.00
9	T C	6.08	2.92	9.00	-3.16	-3.16
10	C T	0.50	24.00	24.50	23.50	-23.50
11	C T	3.25	6.08	9.33	2.83	-2.83
12	C T	3.05	5.65	8.70	2.60	-2.60
13	T C	6.33	1.00	7.33	-5.33	-5.33
14	T C	11.72	1.05	12.77	-10.67	-10.67
15	C T	6.13	3.32	9.45	-2.81	2.81
16	C T	2.05	.	.	.	.
17	T C	2.08	5.90	7.98	3.82	3.82
18	T C	11.68	3.00	14.68	-8.68	-8.68
19	C T	6.12	6.07	12.19	-0.05	0.05
20	T C	3.08	2.10	5.18	-0.98	-0.98
21	C T	24.00	6.05	30.05	-17.95	17.95
22	C T	2.00	6.05	8.05	4.05	-4.05
23	C T	2.00	.	.	.	.
Mean/Median*		5.52	5.78	9.00	-0.98	-3.47
STD		5.18	6.58	7.81	9.32	8.40

Table A 47: Period sums, period differences, and cross-over differences for log($AUC_{0\rightarrow 24}$) for sum of all isoflavones.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	6.29	.	.	.
2	T C	5.46	6.95	12.41	1.49	1.49
3	T C	5.76	6.80	12.56	1.05	1.05
4	T C	.	.	.	.	.
5	C T	6.28	6.54	12.83	0.26	-0.26
6	C T	7.01	6.19	13.19	-0.82	0.82
7	T C	5.96	5.64	11.59	-0.32	-0.32
8	C T	6.06	4.32	10.39	-1.74	1.74
9	T C	6.36	5.10	11.46	-1.26	-1.26
10	C T	6.25	4.15	10.40	-2.10	2.10
11	C T	6.21	4.57	10.78	-1.63	1.63
12	C T	6.42	6.21	12.63	-0.21	0.21
13	T C	5.92	6.51	12.43	0.59	0.59
14	T C	5.60	6.22	11.82	0.62	0.62
15	C T	6.29	5.81	12.10	-0.48	0.48
16	C T	6.47	.	.	.	.
17	T C	5.85	6.40	12.25	0.54	0.54
18	T C	6.87	6.76	13.63	-0.11	-0.11
19	C T	6.32	6.15	12.47	-0.17	0.17
20	T C	6.63	5.18	11.81	-1.45	-1.45
21	C T	7.23	4.76	11.98	-2.47	2.47
22	C T	6.82	4.57	11.39	-2.25	2.25
23	C T	6.67	.	.	.	.
Mean/Median*		6.31	5.76	12.01	-0.55	0.67
STD		0.46	0.90	0.87	1.17	1.10
CV		7.33	15.64	7.25		

Table A 48: Period sums, period differences, and cross-over differences for log($c\_max_{0\rightarrow 24}$) for sum of all isoflavones.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	6.69	.	.	.
2	T C	5.92	7.62	13.55	1.70	1.70
3	T C	7.36	7.64	15.00	0.27	0.27
4	T C	.	.	.	.	.
5	C T	6.83	6.91	13.74	0.08	-0.08
6	C T	7.33	6.59	13.92	-0.74	0.74
7	T C	6.78	7.18	13.96	0.40	0.40
8	C T	7.52	5.02	12.54	-2.49	2.49
9	T C	6.87	5.89	12.75	-0.98	-0.98
10	C T	7.10	5.23	12.33	-1.87	1.87
11	C T	7.32	5.03	12.35	-2.29	2.29
12	C T	7.11	6.49	13.60	-0.62	0.62
13	T C	6.55	7.66	14.21	1.11	1.11
14	T C	6.08	7.21	13.29	1.13	1.13
15	C T	6.79	6.68	13.47	-0.11	0.11
16	C T	7.53	.	.	.	.
17	T C	6.40	7.24	13.64	0.84	0.84
18	T C	7.44	7.68	15.12	0.25	0.25
19	C T	7.05	6.64	13.70	-0.41	0.41
20	T C	7.29	5.88	13.17	-1.42	-1.42
21	C T	7.67	5.62	13.29	-2.06	2.06
22	C T	7.64	5.37	13.01	-2.27	2.27
23	C T	7.57	.	.	.	.
Mean/Median*		7.05	6.51	13.51	-0.50	0.85
STD		0.50	0.91	0.76	1.29	1.09
CV		7.10	14.01	5.65		

Table A 49: Period sums, period differences, and cross-over differences for t_max$_{0\rightarrow 24}$ for sum of all isoflavones.

snr	Seq.	period I	period II	periods total	period differences	cross over differences
1	T C	.	6.17	.	.	.
2	T C	6.00	2.07	8.07	-3.93	-3.93
3	T C	3.00	0.58	3.58	-2.42	-2.42
4	T C	.	.	.	.	.
5	C T	6.00	11.50	17.50	5.50	-5.50
6	C T	6.00	14.00	20.00	8.00	-8.00
7	T C	5.52	3.05	8.57	-2.47	-2.47
8	C T	1.08	6.08	7.16	5.00	-5.00
9	T C	6.08	2.00	8.08	-4.08	-4.08
10	C T	0.50	24.00	24.50	23.50	-23.50
11	C T	3.25	11.62	14.87	8.37	-8.37
12	C T	3.05	5.65	8.70	2.60	-2.60
13	T C	6.33	1.00	7.33	-5.33	-5.33
14	T C	11.72	0.58	12.30	-11.14	-11.14
15	C T	6.13	3.32	9.45	-2.81	2.81
16	C T	2.05	.	.	.	.
17	T C	2.08	5.90	7.98	3.82	3.82
18	T C	11.68	3.00	14.68	-8.68	-8.68
19	C T	6.12	6.07	12.19	-0.05	0.05
20	T C	3.08	2.10	5.18	-0.98	-0.98
21	C T	3.02	2.00	5.02	-1.02	1.02
22	C T	6.00	6.05	12.05	0.05	-0.05
23	C T	2.00	.	.	.	.
Mean/Median*		5.52	4.49	8.70	-0.98	-3.93
STD		2.99	5.72	5.43	7.58	6.10

Table A 50: Bioequivalence intervals for the log-transformed values of $AUC_{0\rightarrow 24}$ and $c\_max_{0\rightarrow 24}$ for daidzein, genistein, and sum of all isoflavones, calculated for the formulations given in period I.

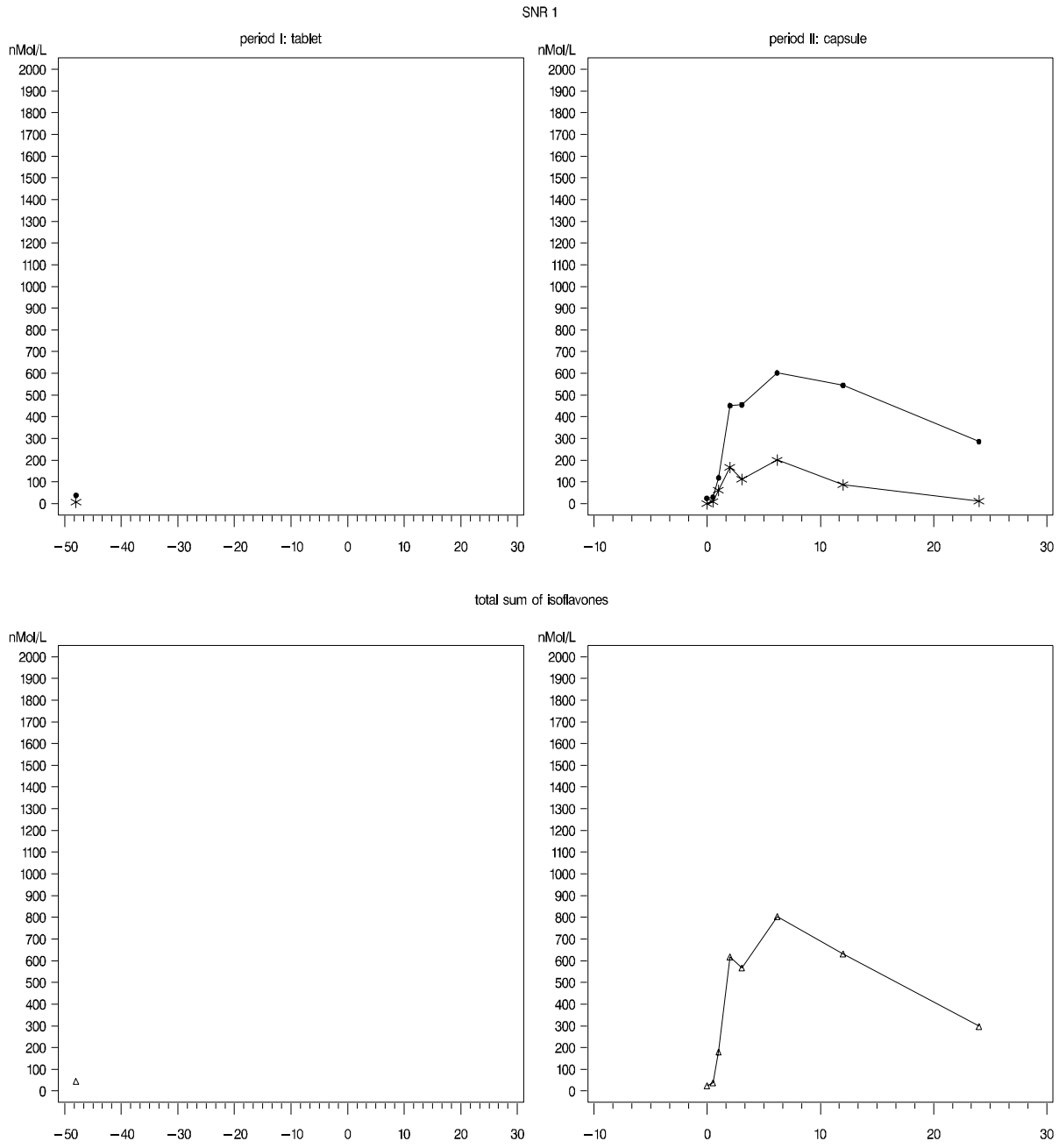
parameter	lower bound estimation	ratio "capsule/tablet"	upper bound estimation
daidzein: $\ln(AUC_{0\rightarrow 24})$	0.898	1.210	1.631
daidzein: $\ln(c\_max_{0\rightarrow 24})$	1.119	1.698	2.577
genistein: $\ln(AUC_{0\rightarrow 24})$	1.136	1.686	2.501
genistein: $\ln(c\_max_{0\rightarrow 24})$	1.117	1.728	2.672
sum of all isoflavones: $\ln(AUC_{0\rightarrow 24})$	1.105	1.560	2.204
sum of all isoflavones: $\ln(c\_max_{0\rightarrow 24})$	1.148	1.636	2.331

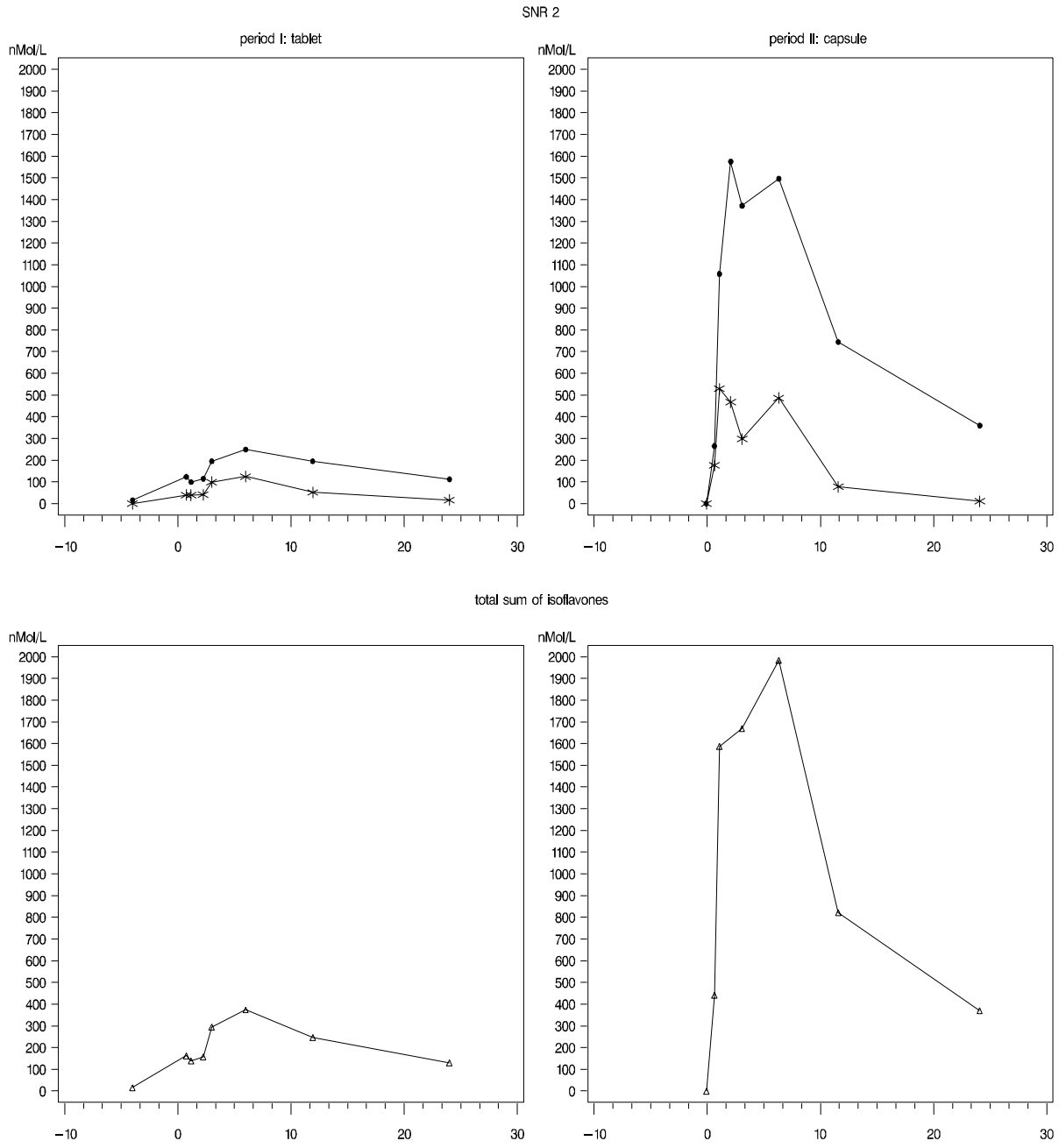
Table A 51: Non parametric 90% confidence limits for the difference "capsule-tablet" of the parameter $t\_max_{0\rightarrow 24}$ for daidzein, genistein, and sum of all isoflavones.

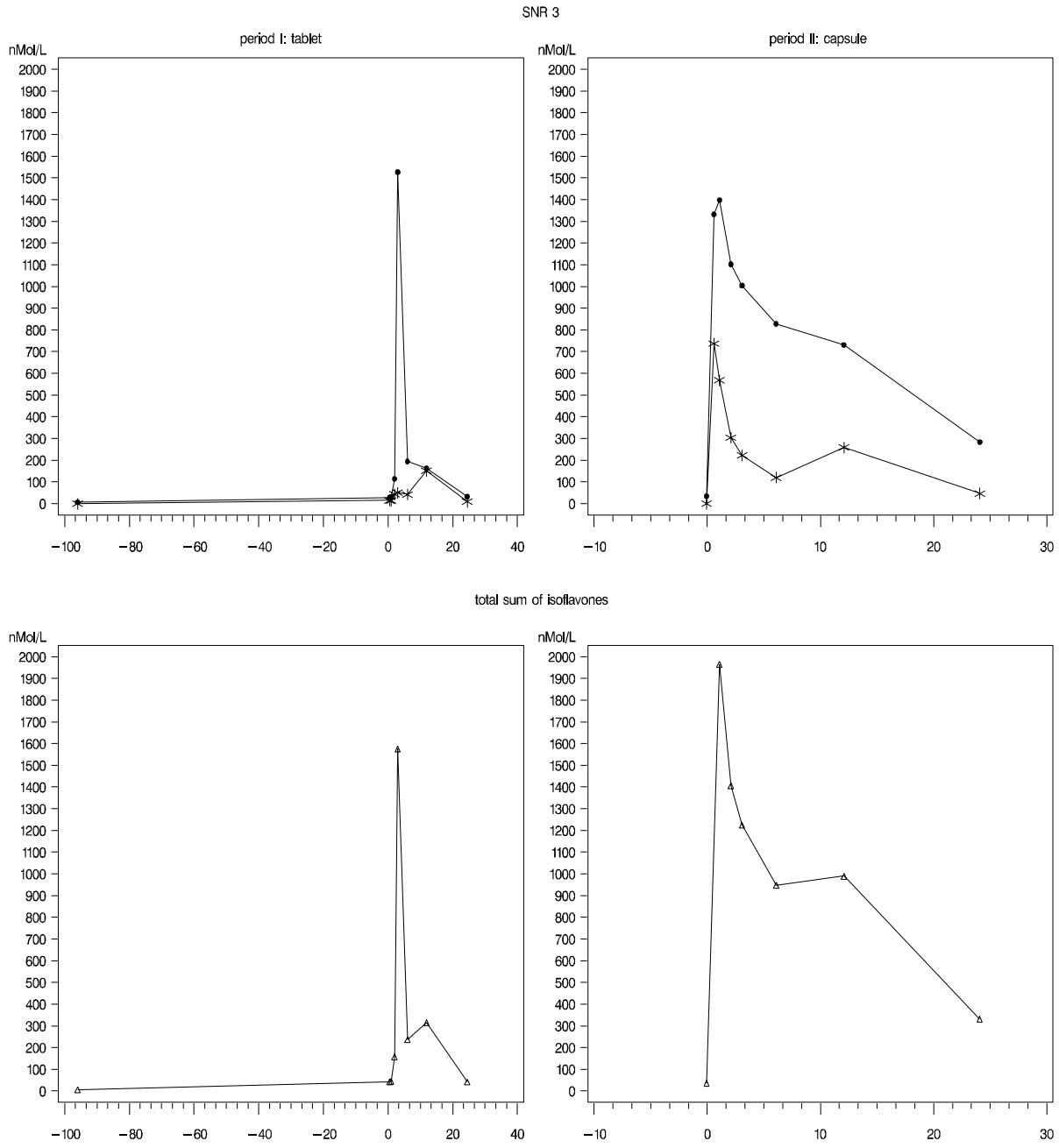
parameter	lower bound estimation	difference	upper bound estimation
daidzein: $t\_max_{0\rightarrow 24}$	-5.79	-3.34	-0.08
genistein: $t\_max_{0\rightarrow 24}$	-4.92	-1.00	0.60
sum of all isoflavones: $t\_max_{0\rightarrow 24}$	-5.02	-1.29	0.17

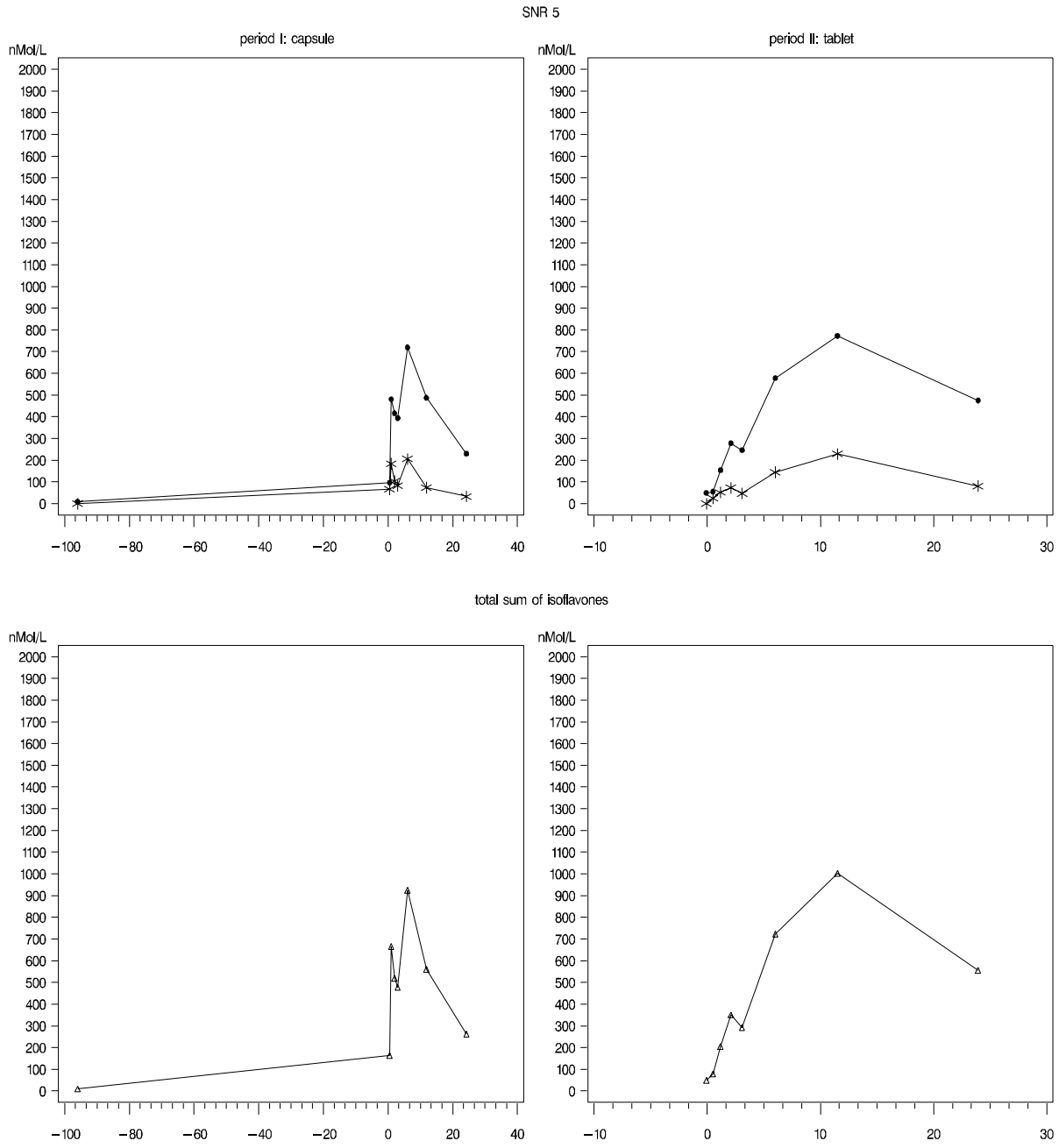
8.2 List of Figures

Figure A 1: Concentration-time profiles for daidzein, genistein, and sum of all isoflavones for all study subjects (period I and day 1 of period II).
Legend: * = daidzein, • = genistein, Δ = total sum of isoflavones.

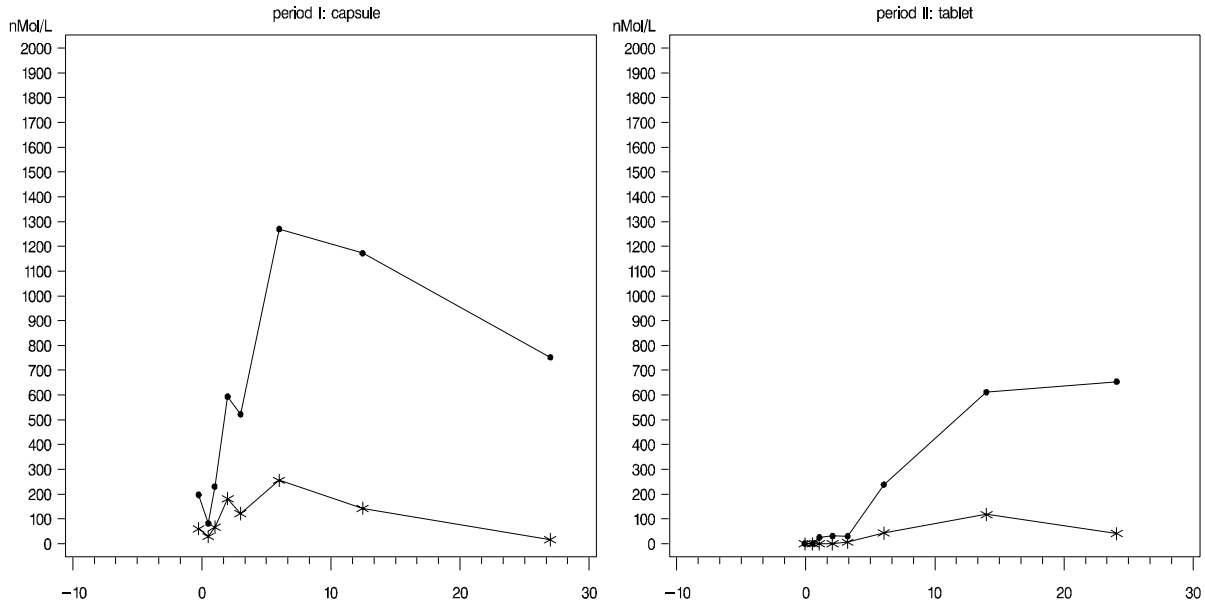



SNR 2
period I: tablet
period II: capsule
nMol/L
total sum of isoflavones

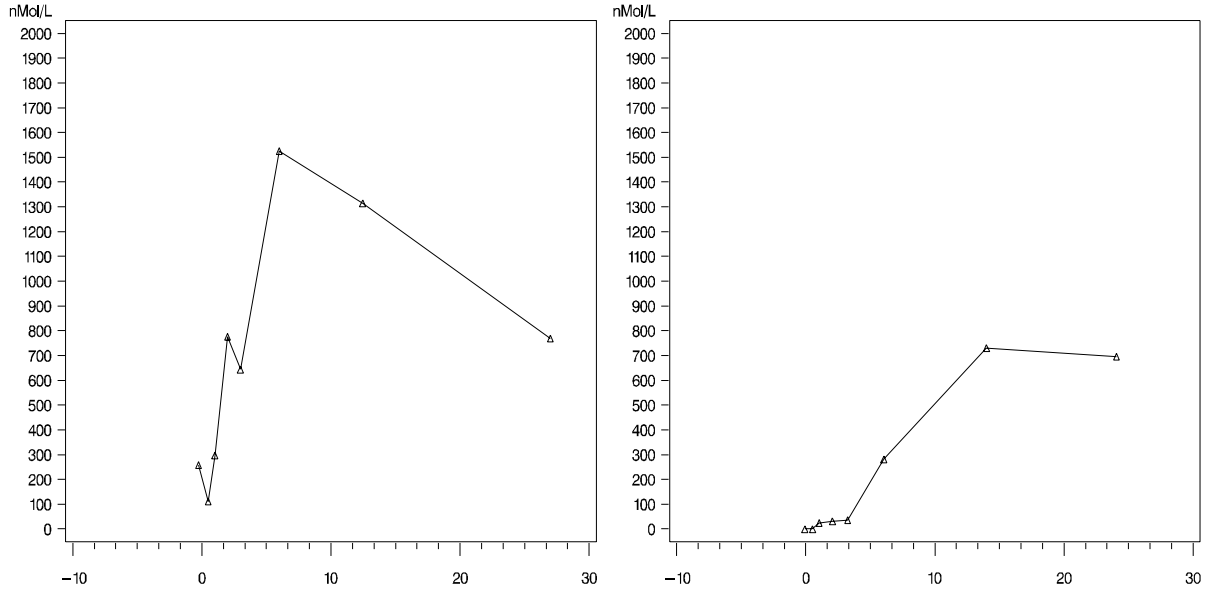

SNR 3
period I: tablet
period II: capsule
nMol/L
total sum of isoflavones


SNR 5
period I: capsule
period II: tablet
nMol/L
total sum of isoflavones

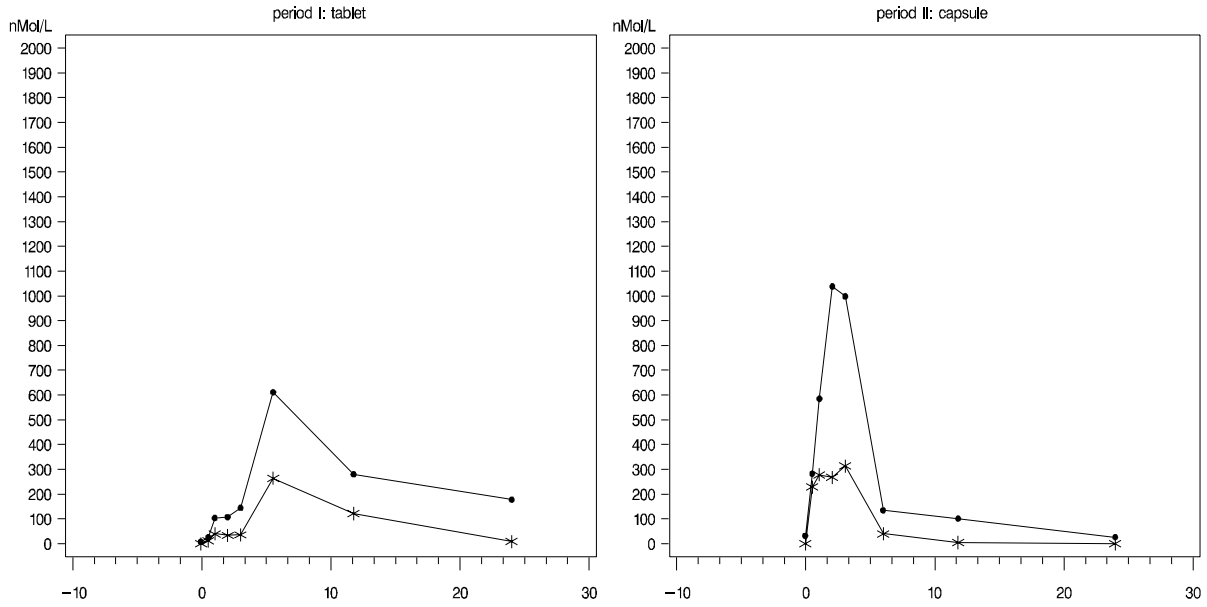
SNR 6



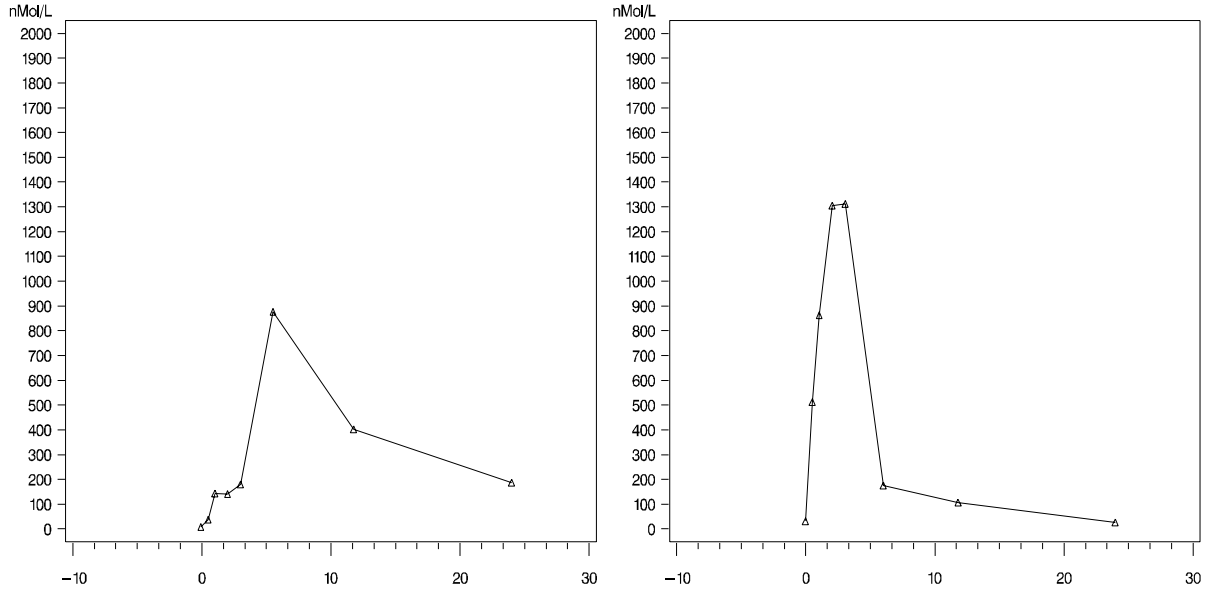
total sum of isoflavones



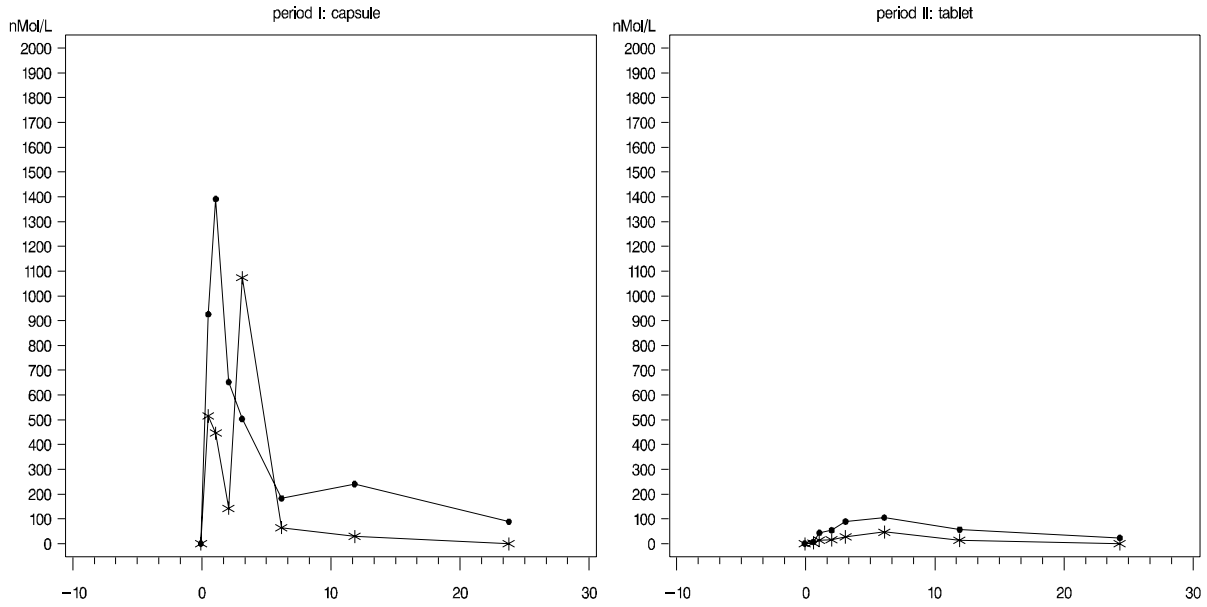
SNR 7



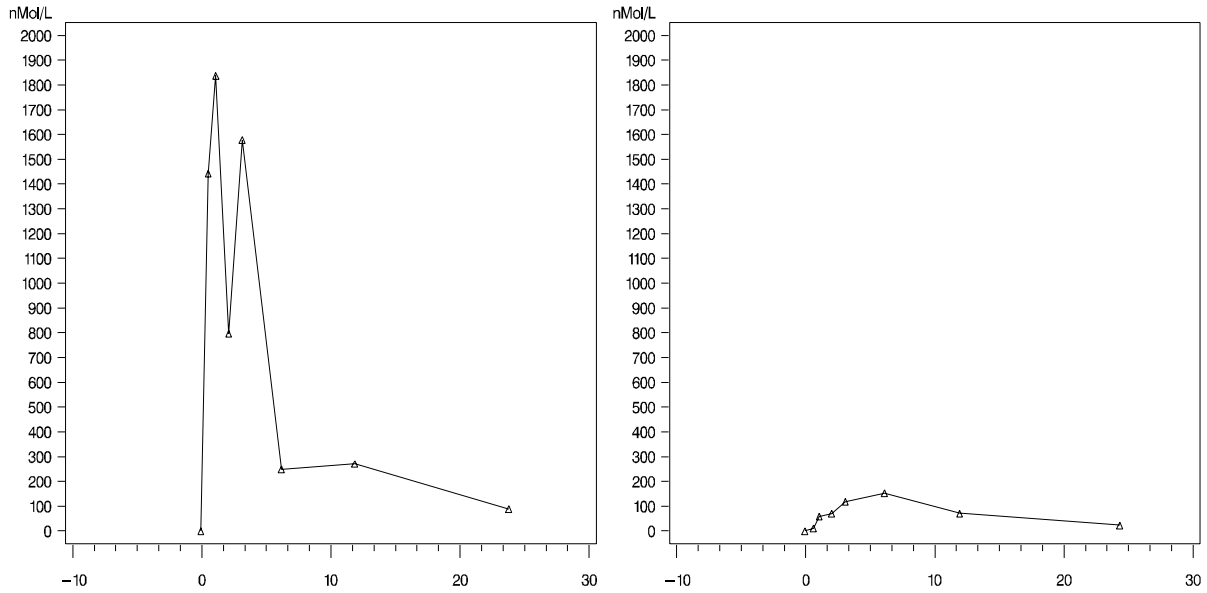
total sum of isoflavones

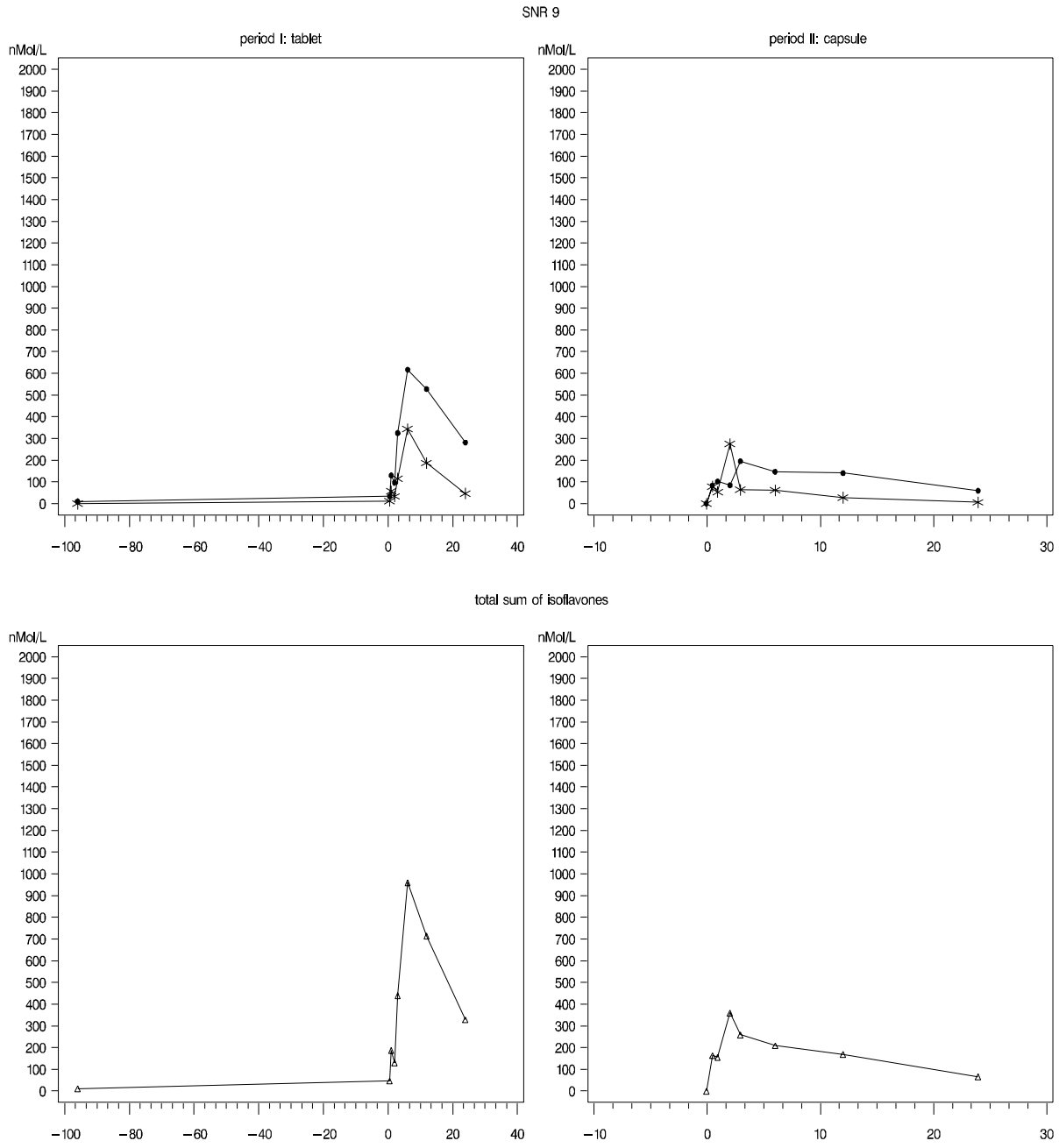


SNR 8

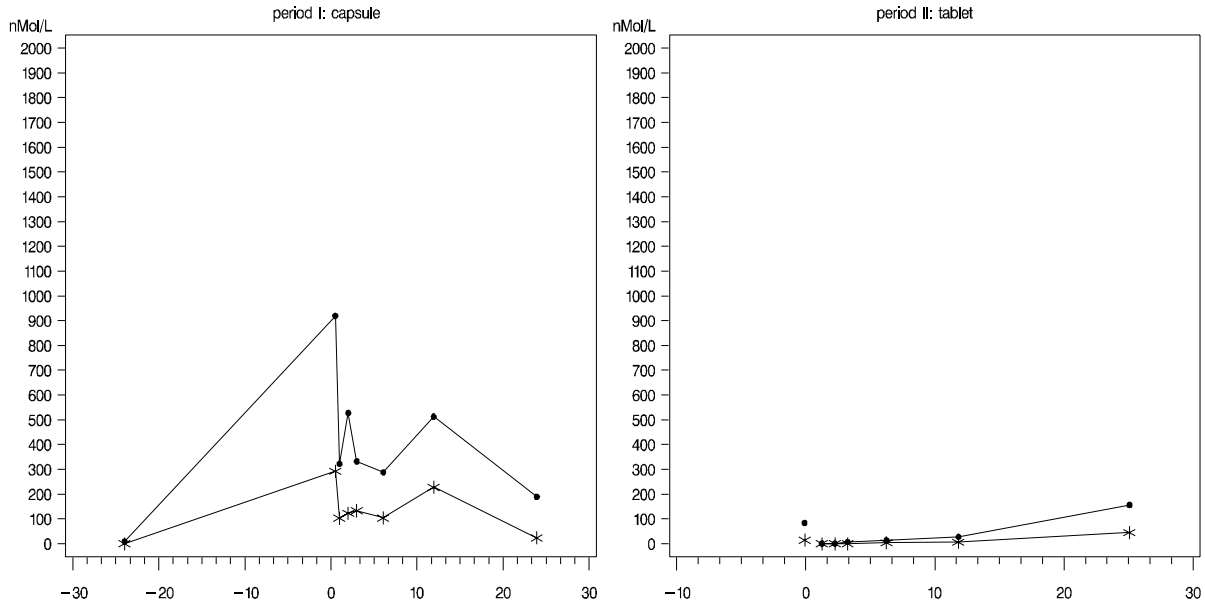


total sum of isoflavones

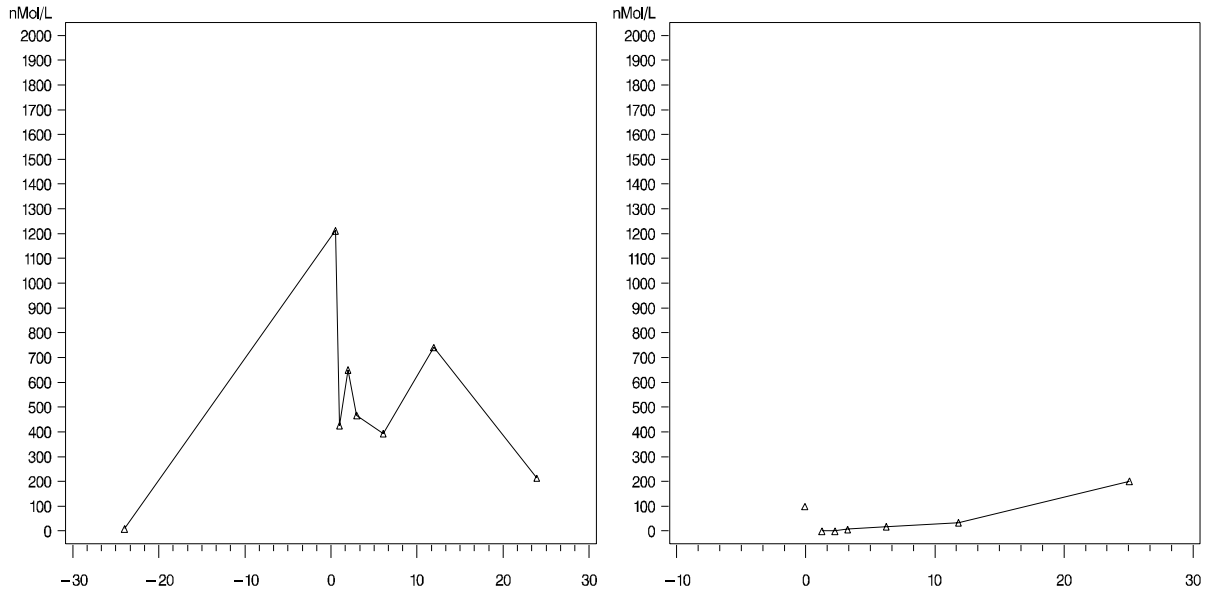


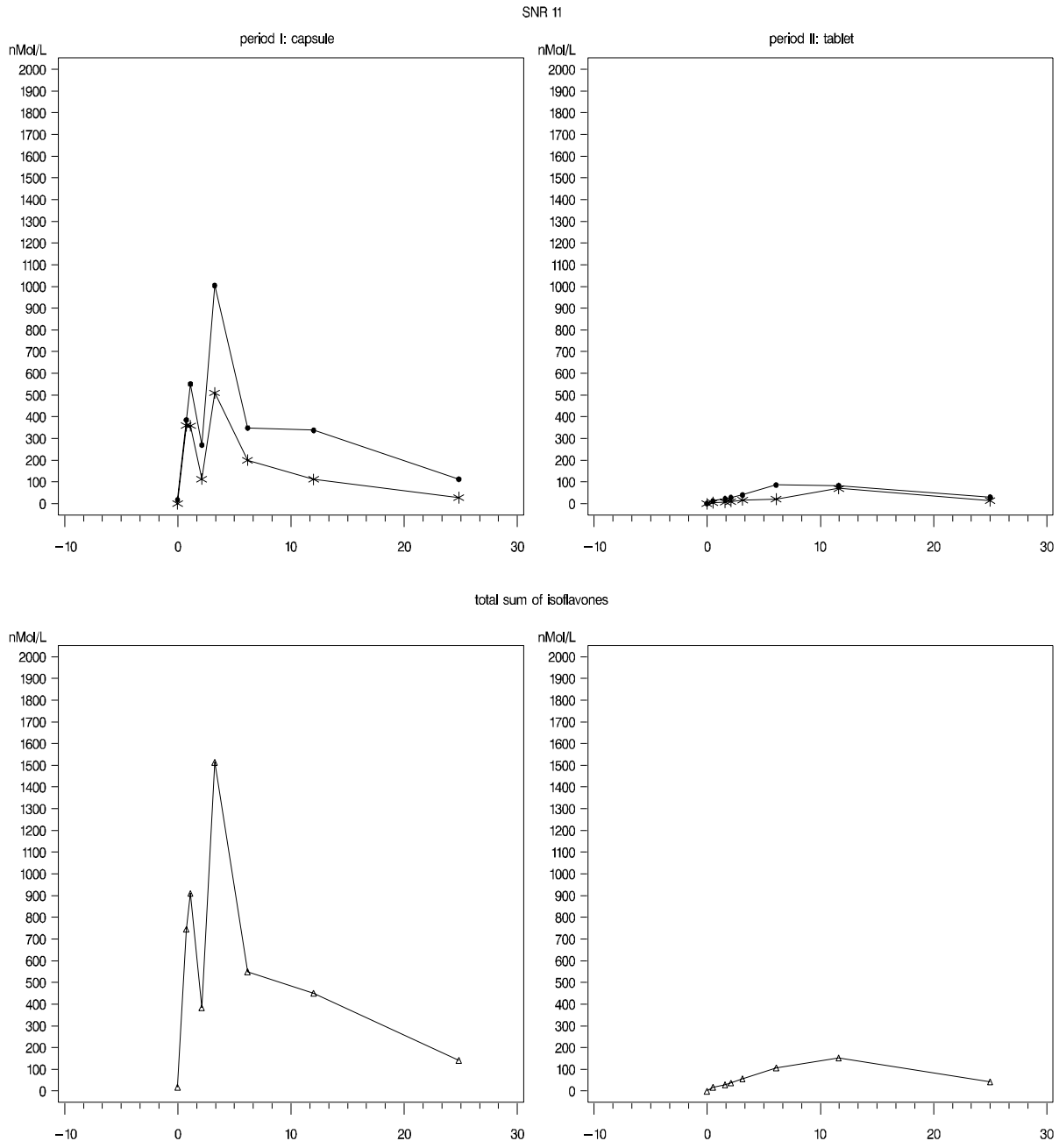

SNR 9
period I: tablet
period II: capsule
nMol/L
total sum of isoflavones

SNR 10

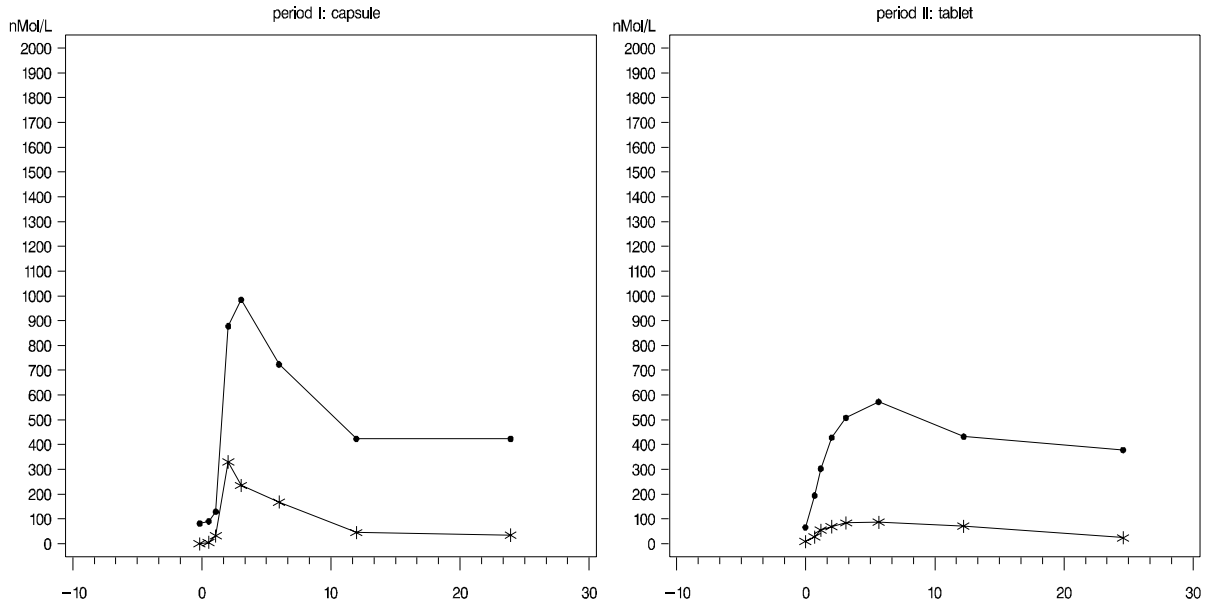


total sum of isoflavones

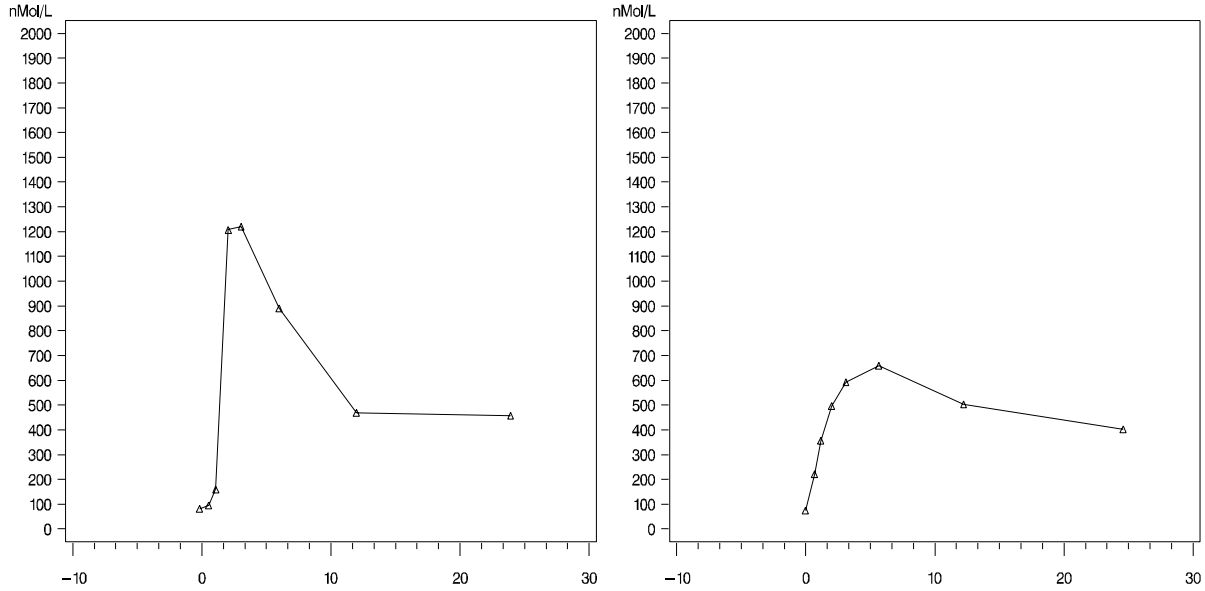


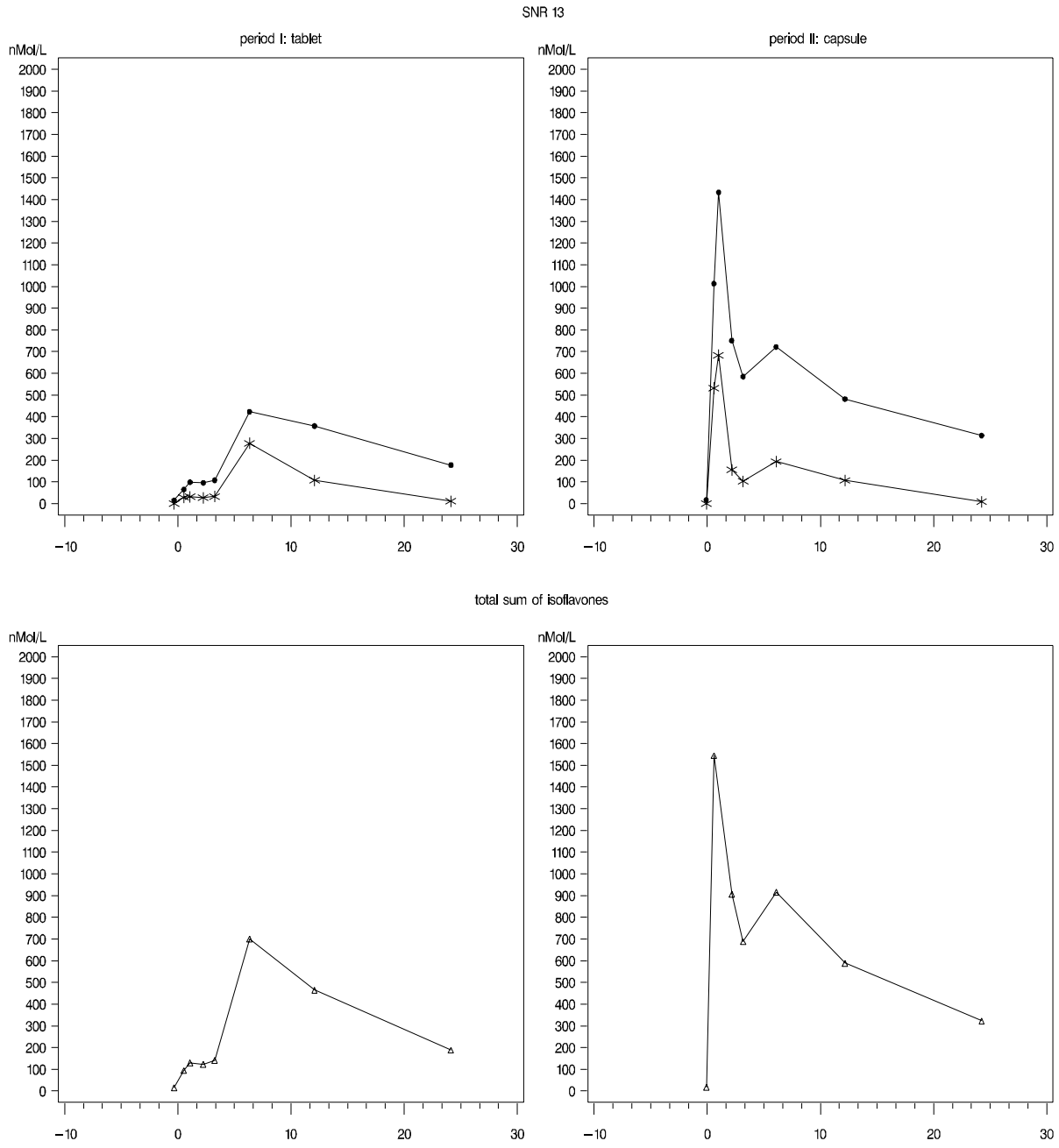

SNR 11
period I: capsule
period II: tablet
nMol/L
total sum of isoflavones

SNR 12

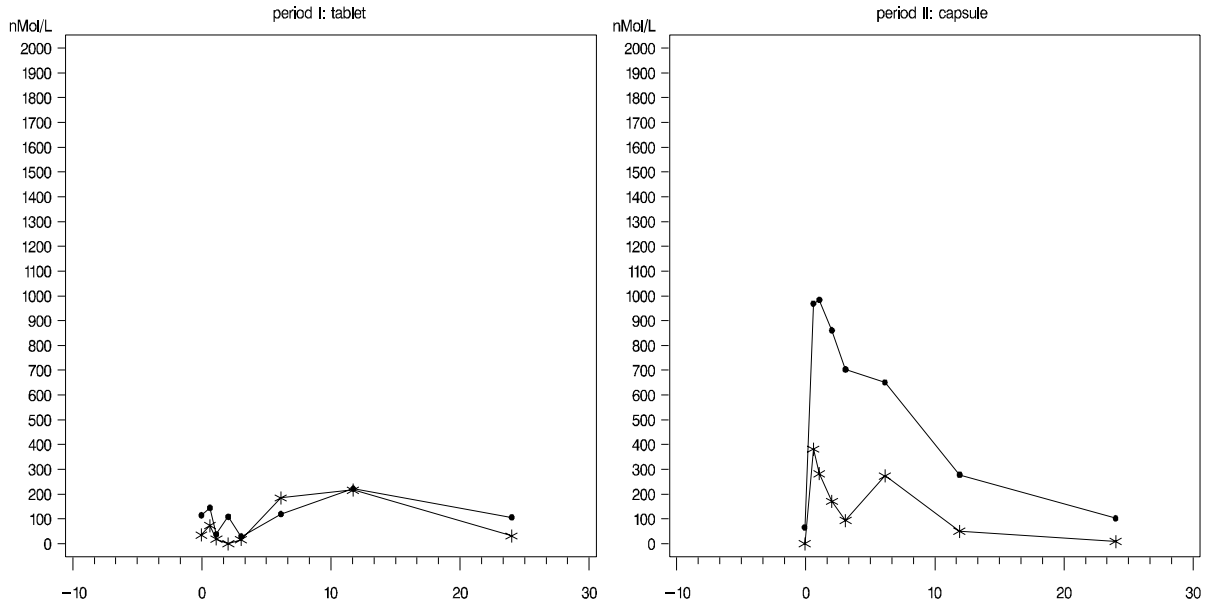


total sum of isoflavones

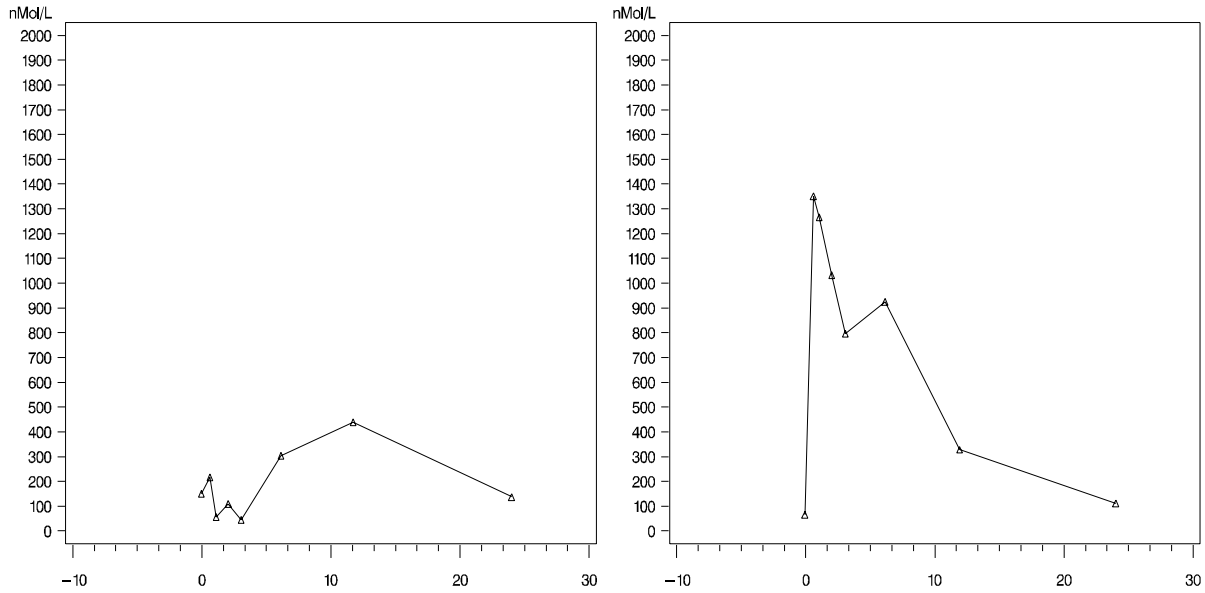



SNR 13
period I: tablet
period II: capsule
nMol/L
total sum of isoflavones

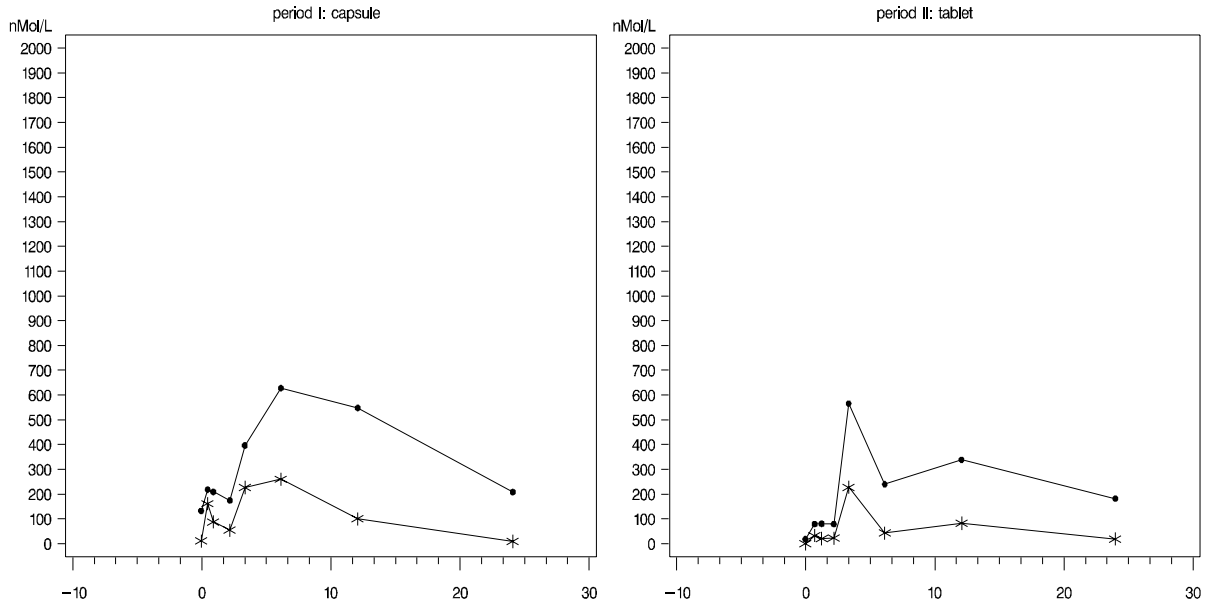
SNR 14



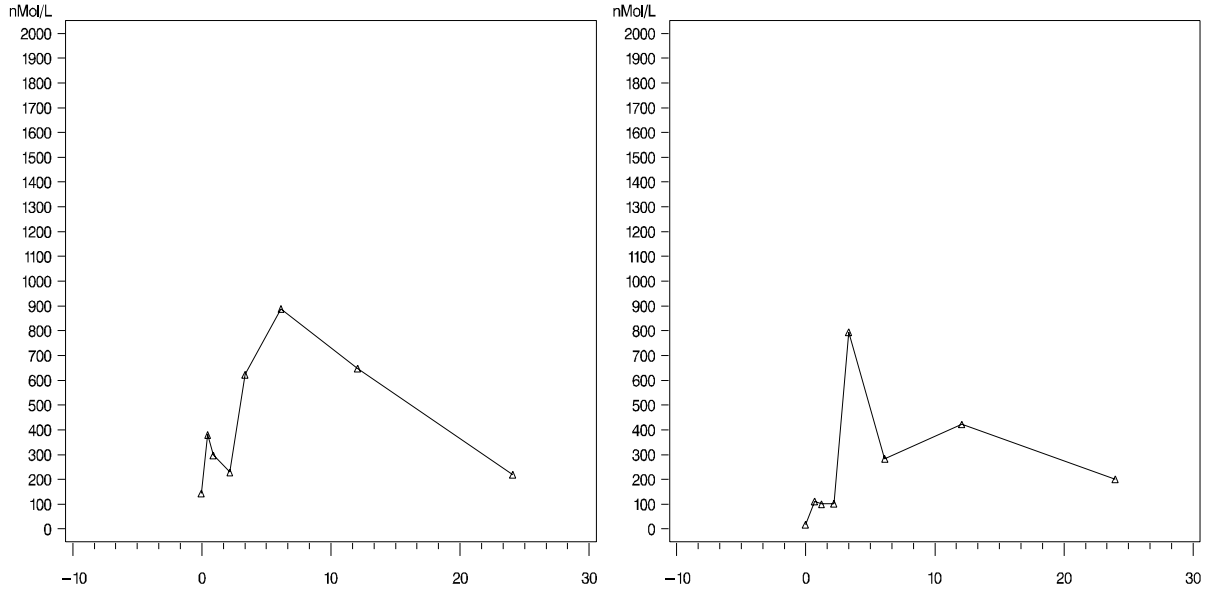
total sum of isoflavones



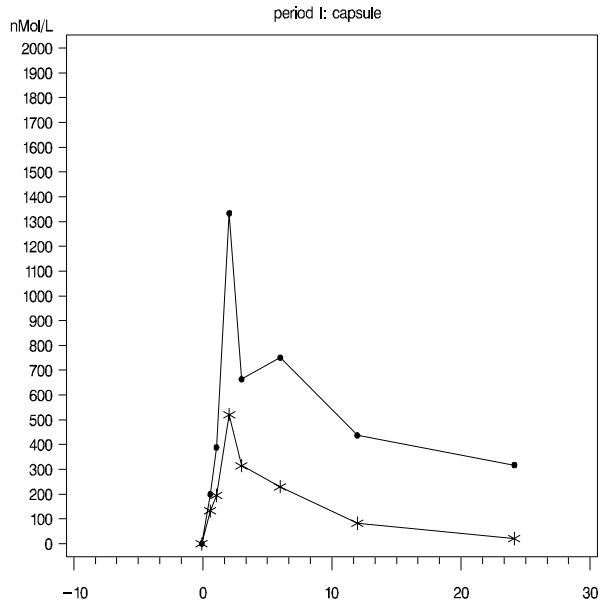
SNR 15

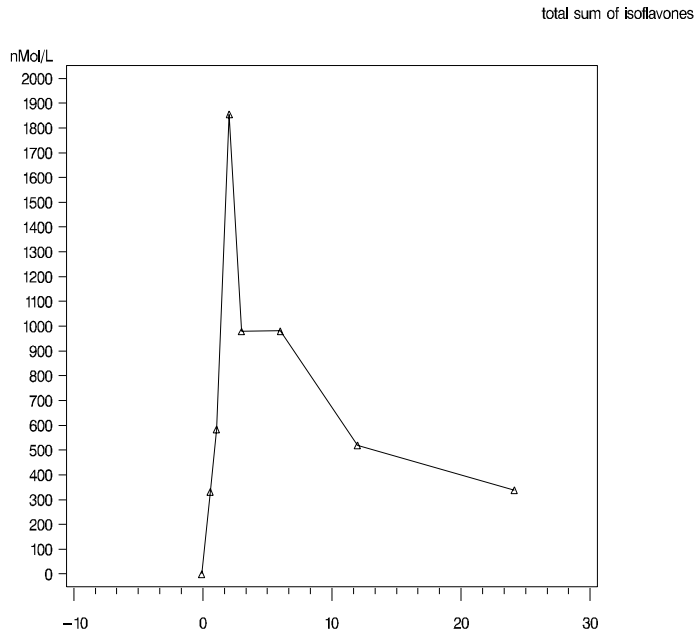


total sum of isoflavones

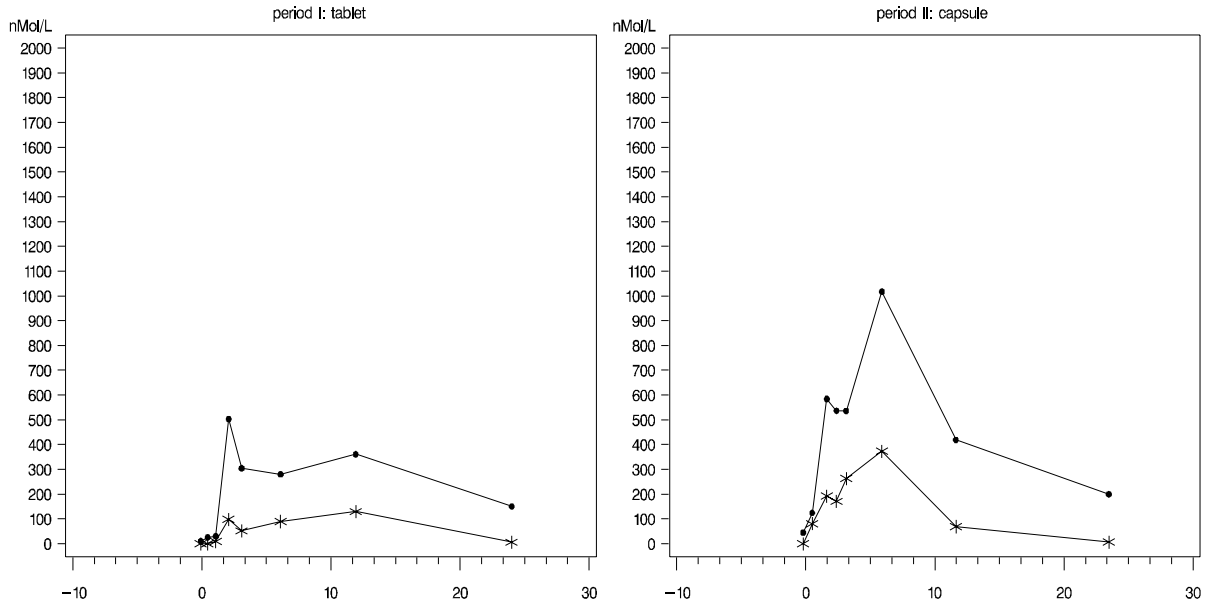


SNR 16

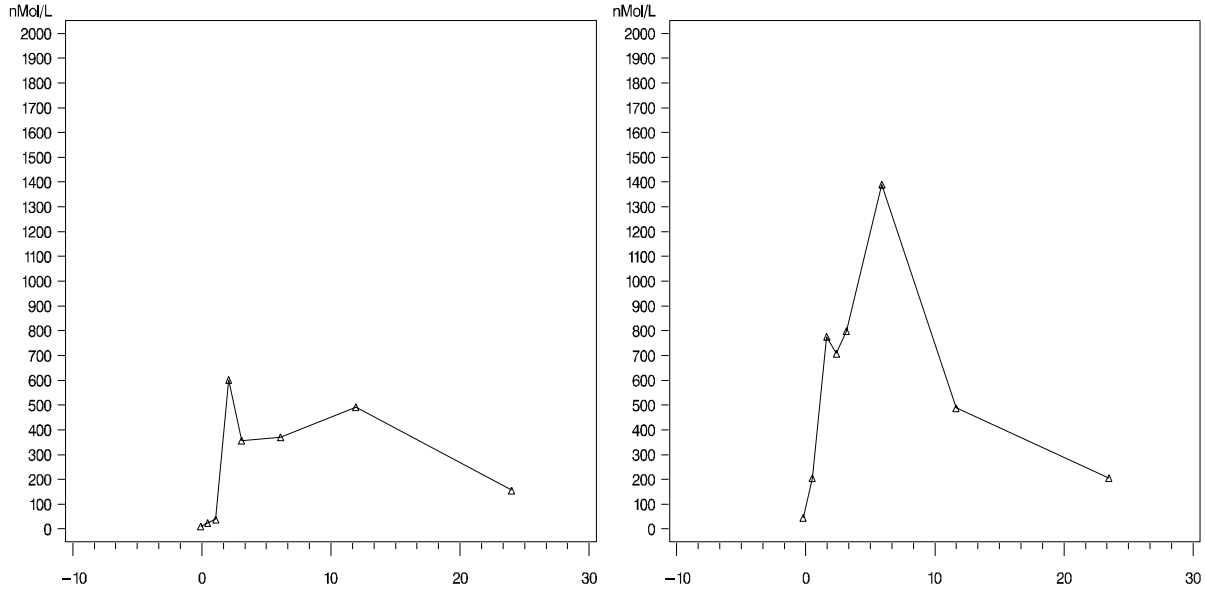

period I: capsule
nMol/L
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−10
0
10
20
30

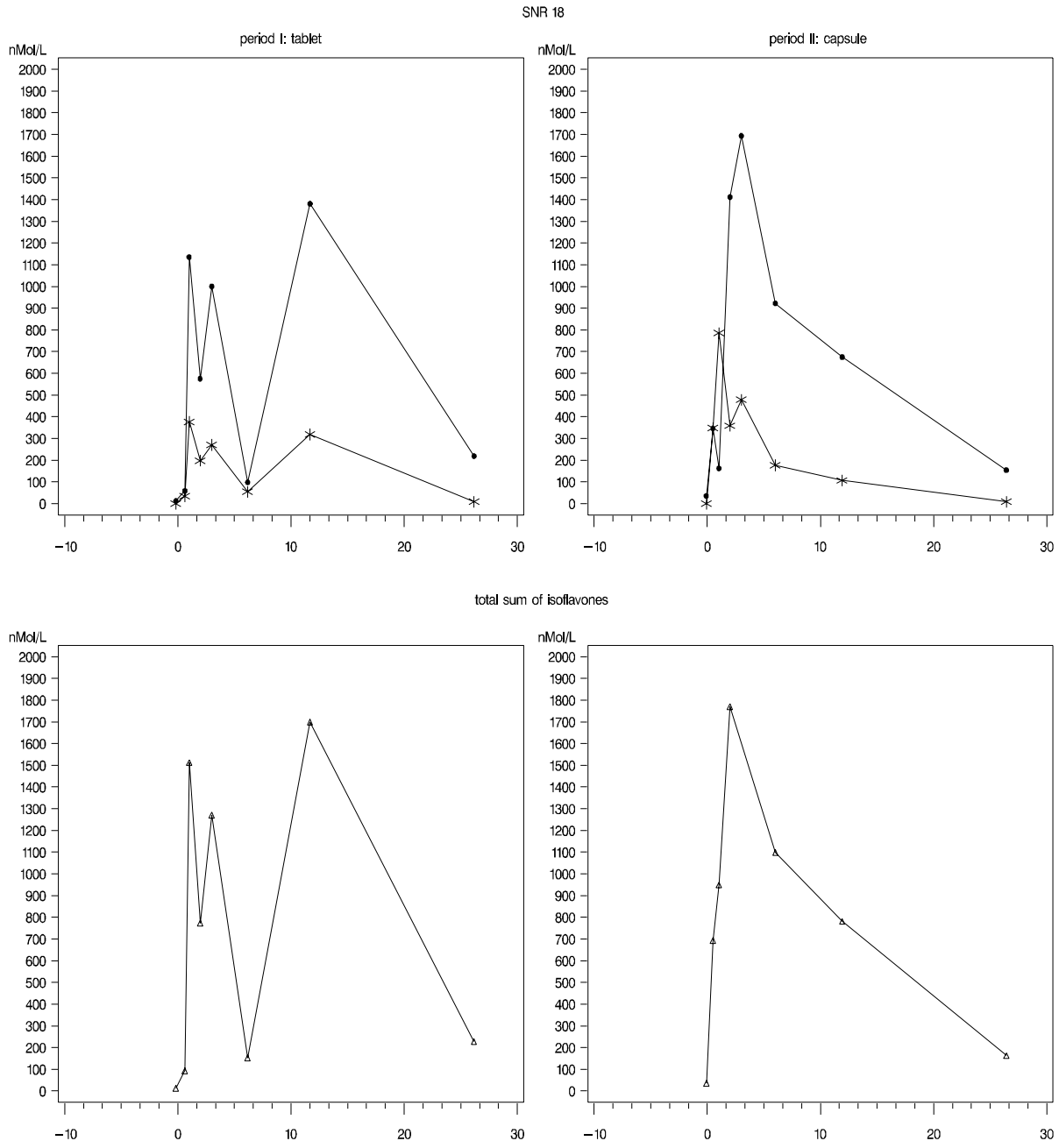

total sum of isoflavones
nMol/L
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−10
0
10
20
30

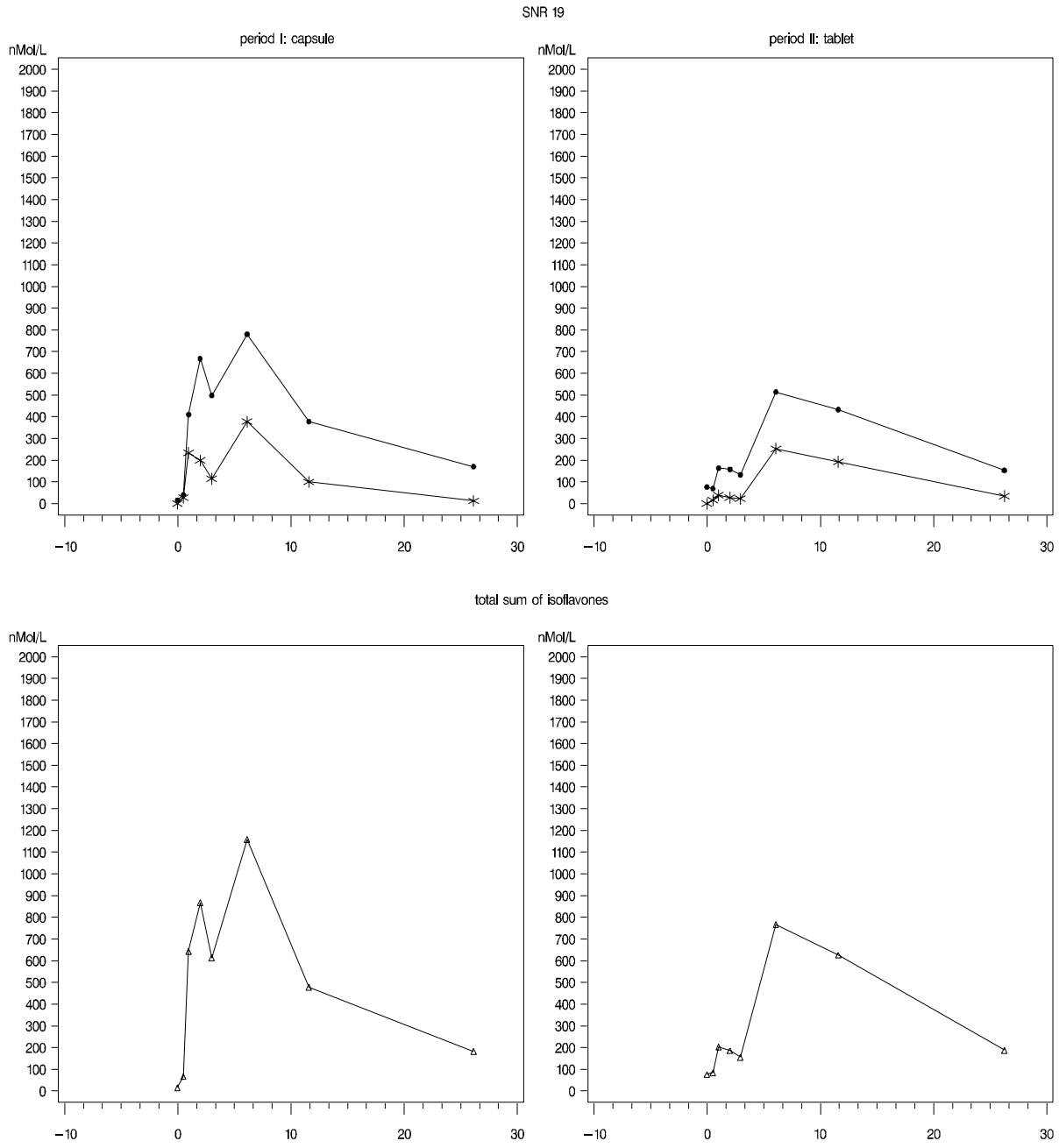
SNR 17

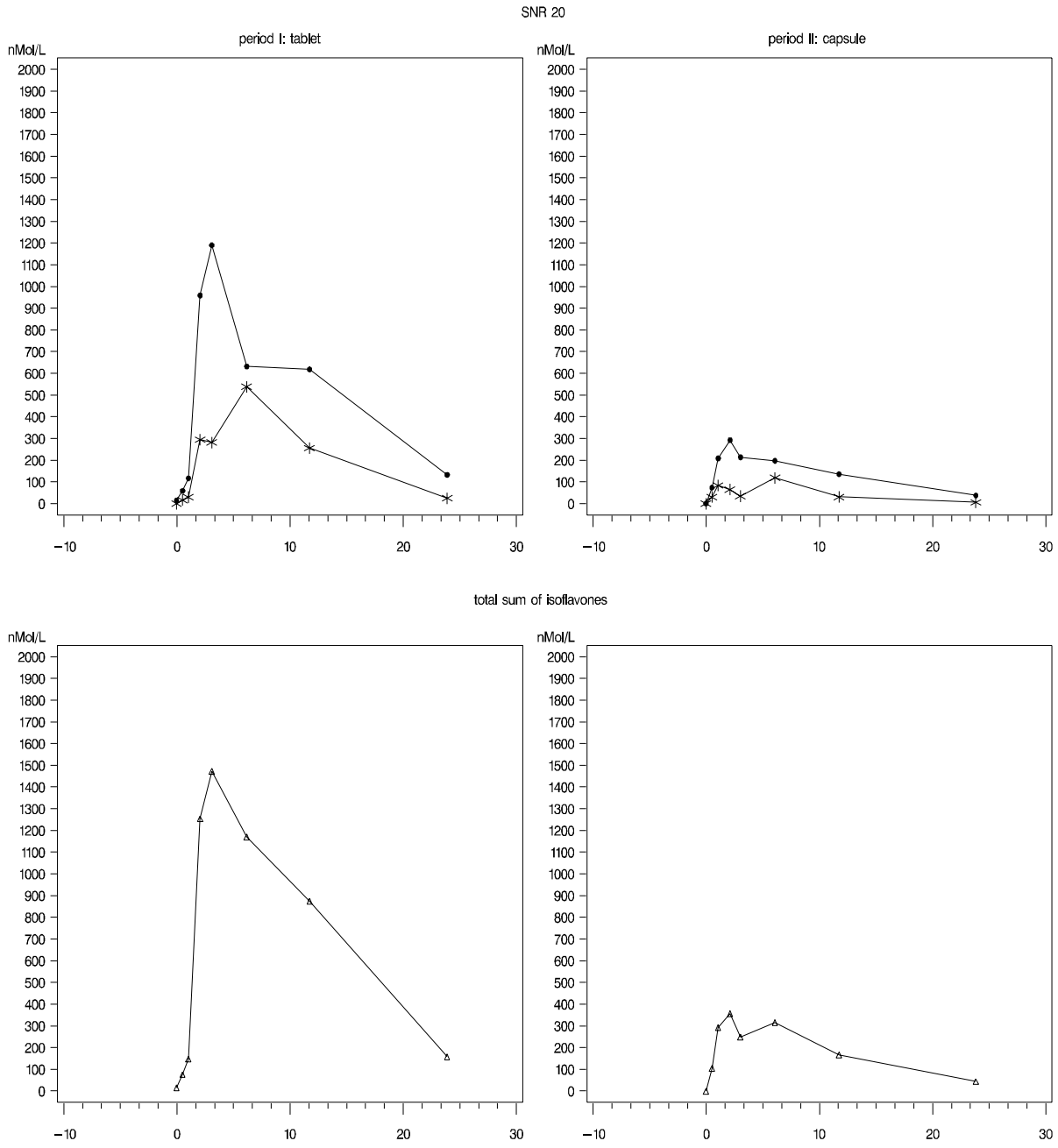


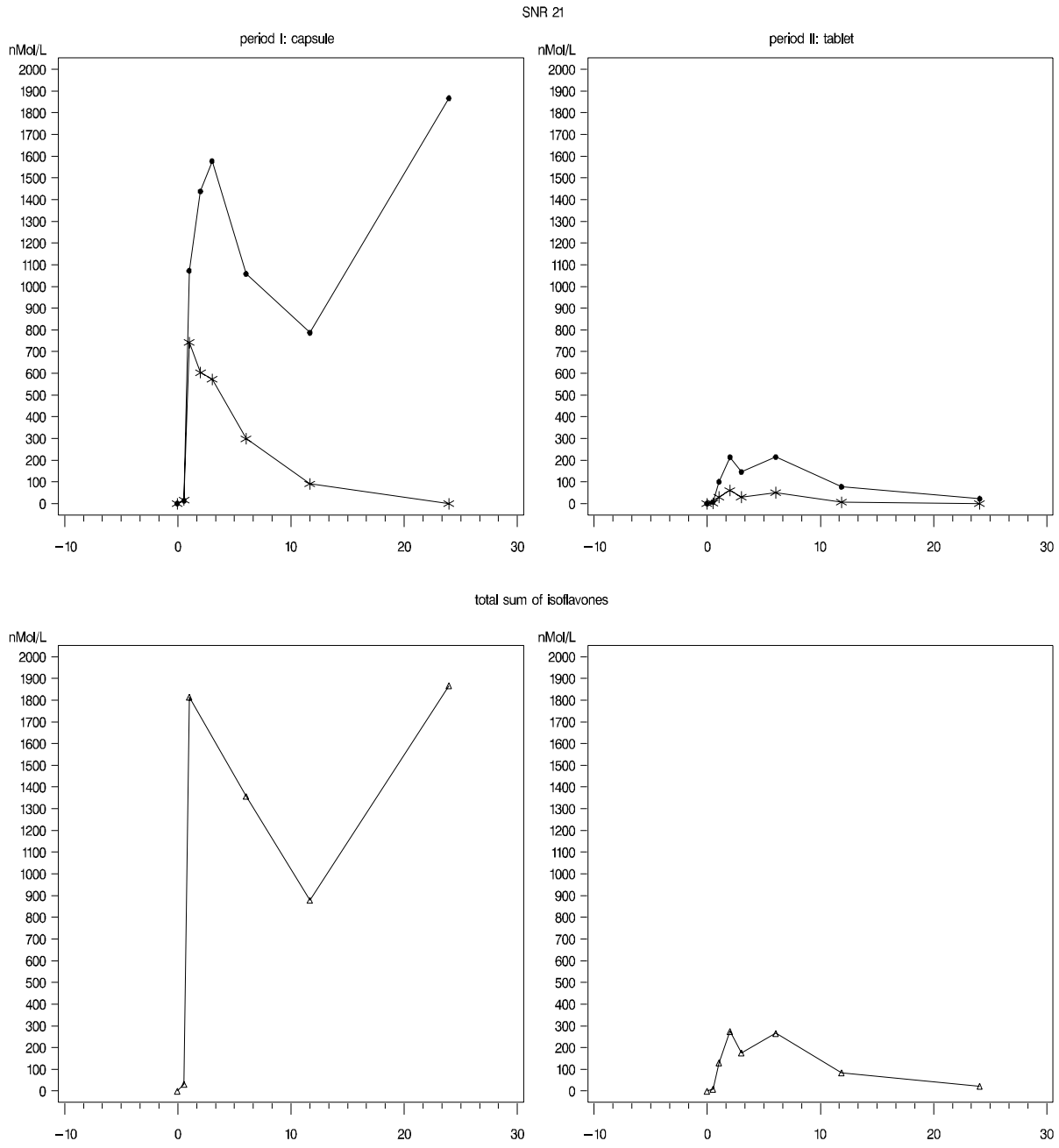
total sum of isoflavones



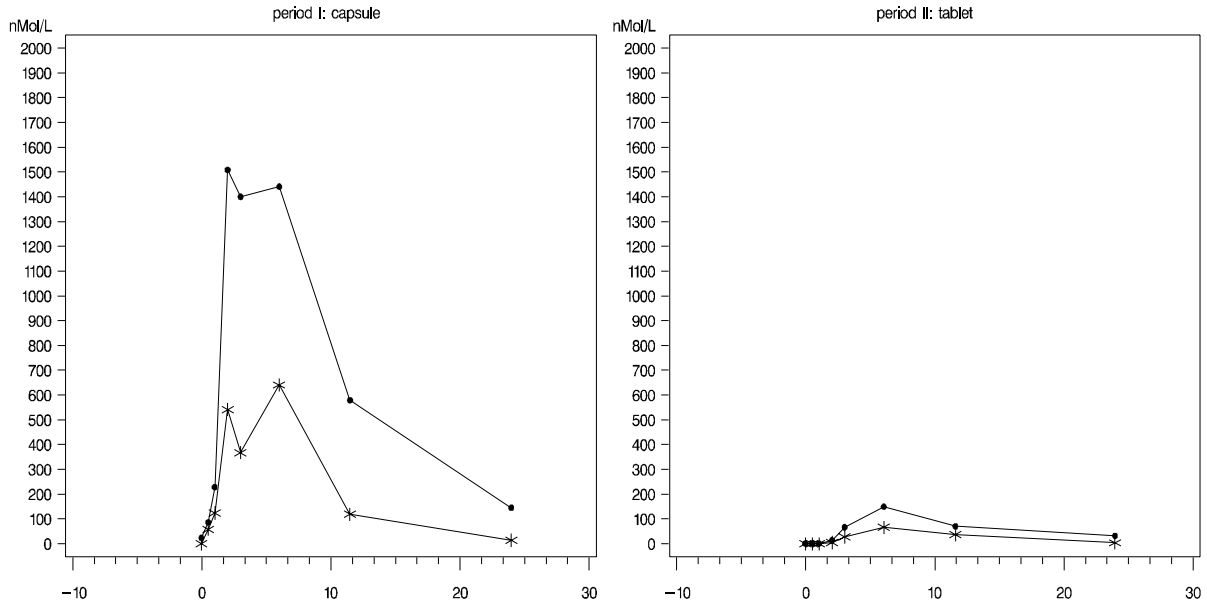

SNR 18
period I: tablet
period II: capsule
nMol/L
total sum of isoflavones


SNR 19
period I: capsule
period II: tablet
nMol/L
total sum of isoflavones

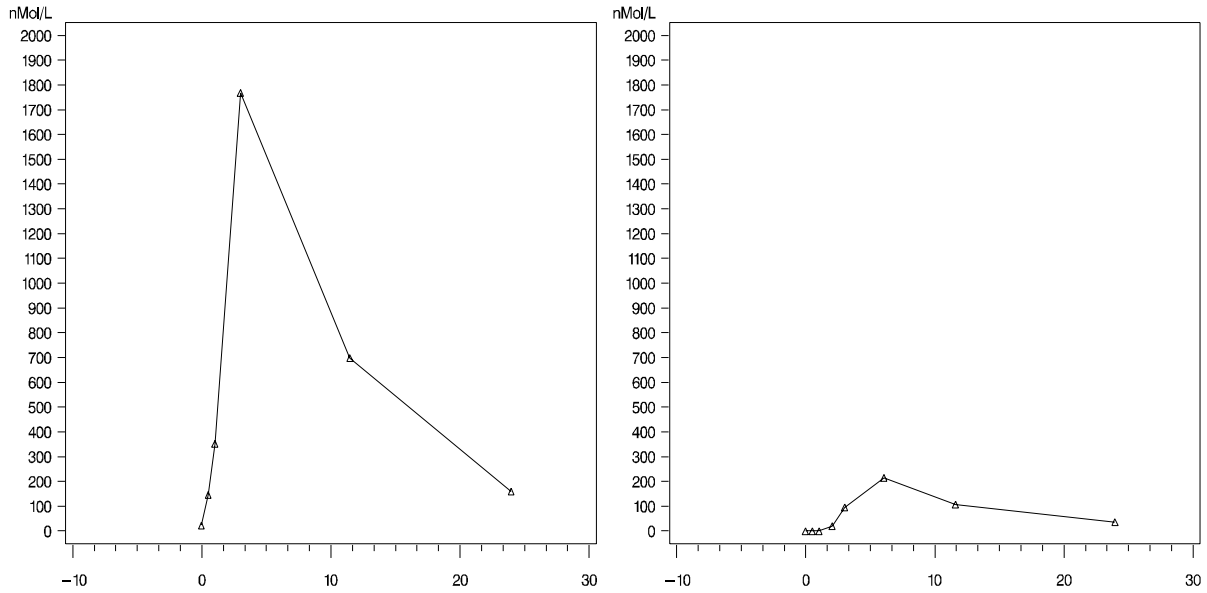

SNR 20
period I: tablet
period II: capsule
nMol/L
total sum of isoflavones


SNR 21
period I: capsule
period II: tablet
nMol/L
total sum of isoflavones

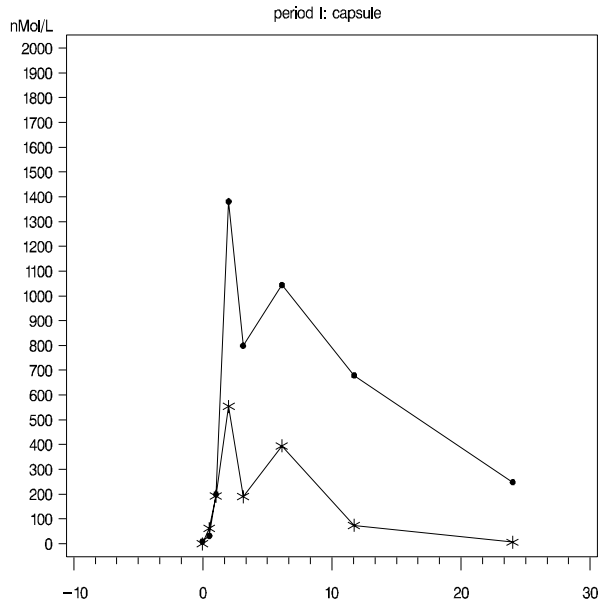
SNR 22



total sum of isoflavones



SNR 23


period I: capsule
nMol/L
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−10
0
10
20
30

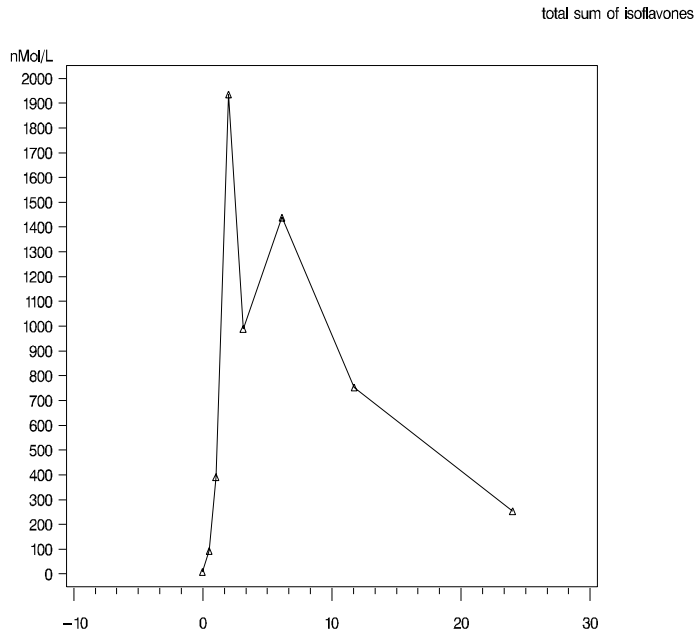
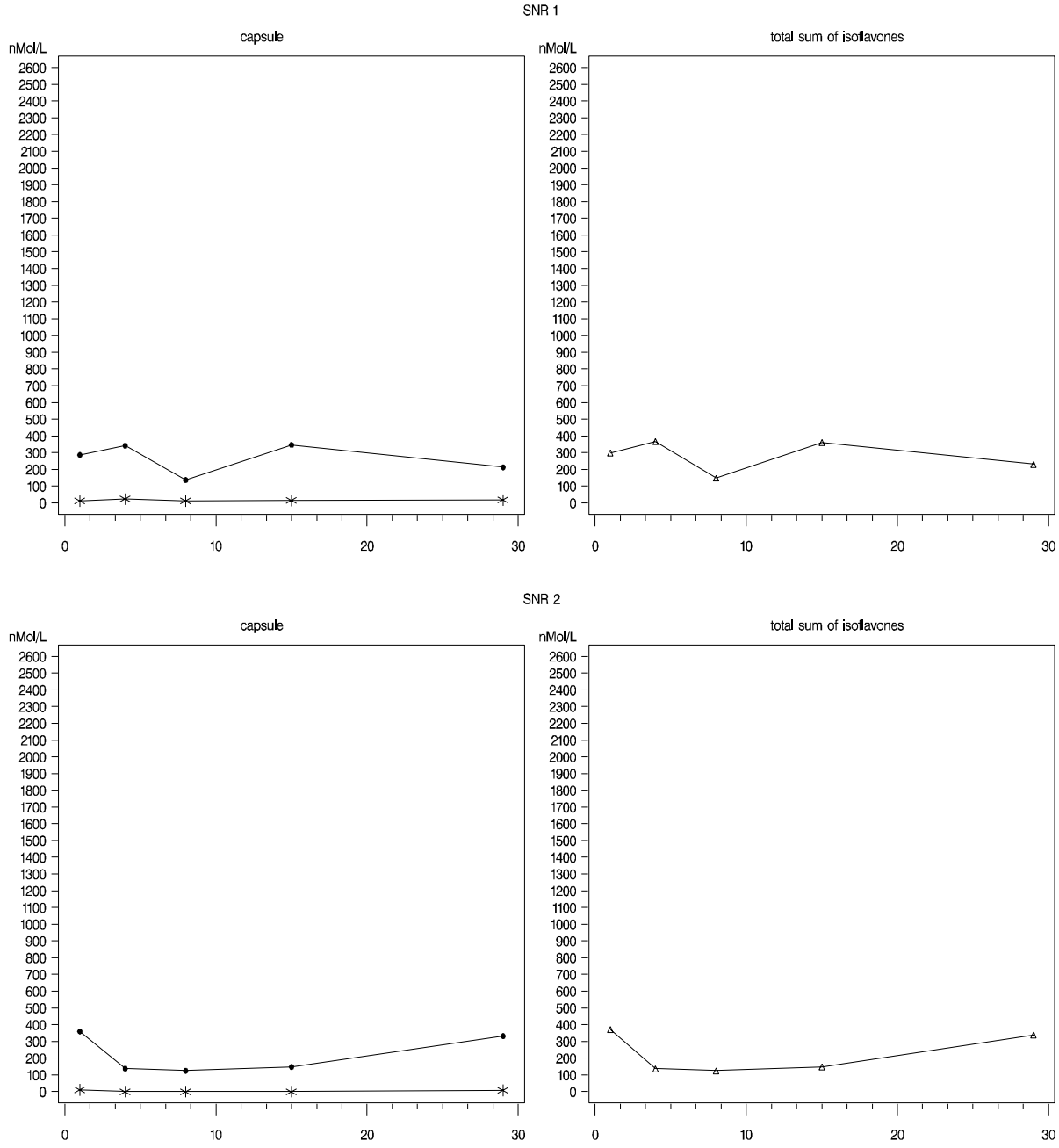
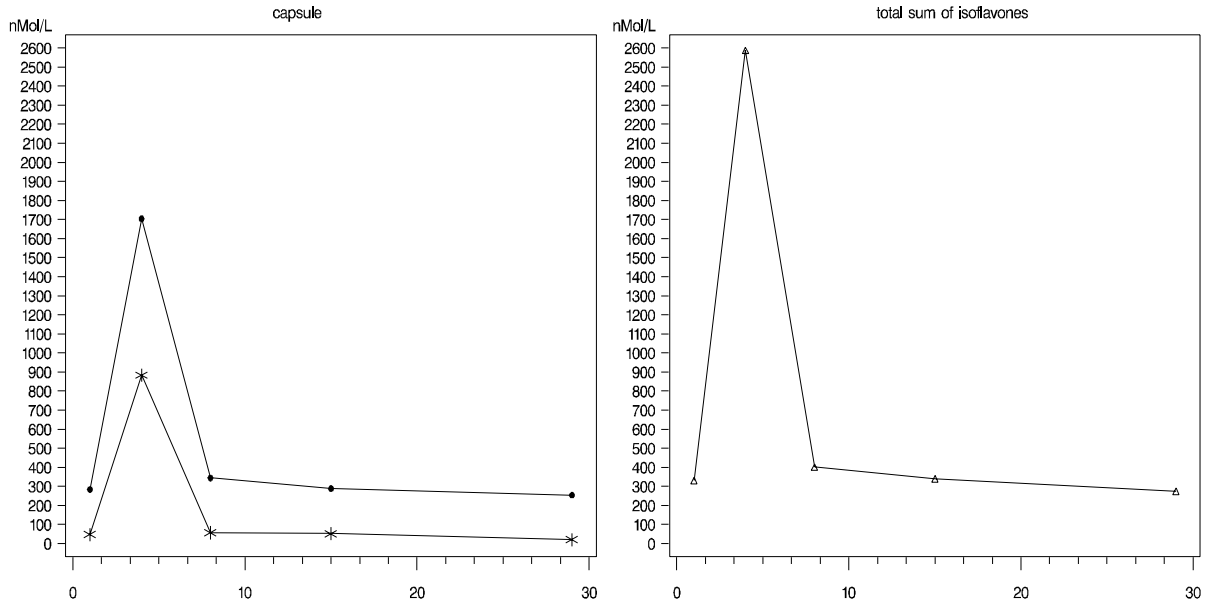

total sum of isoflavones
nMol/L
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−10
0
10
20
30

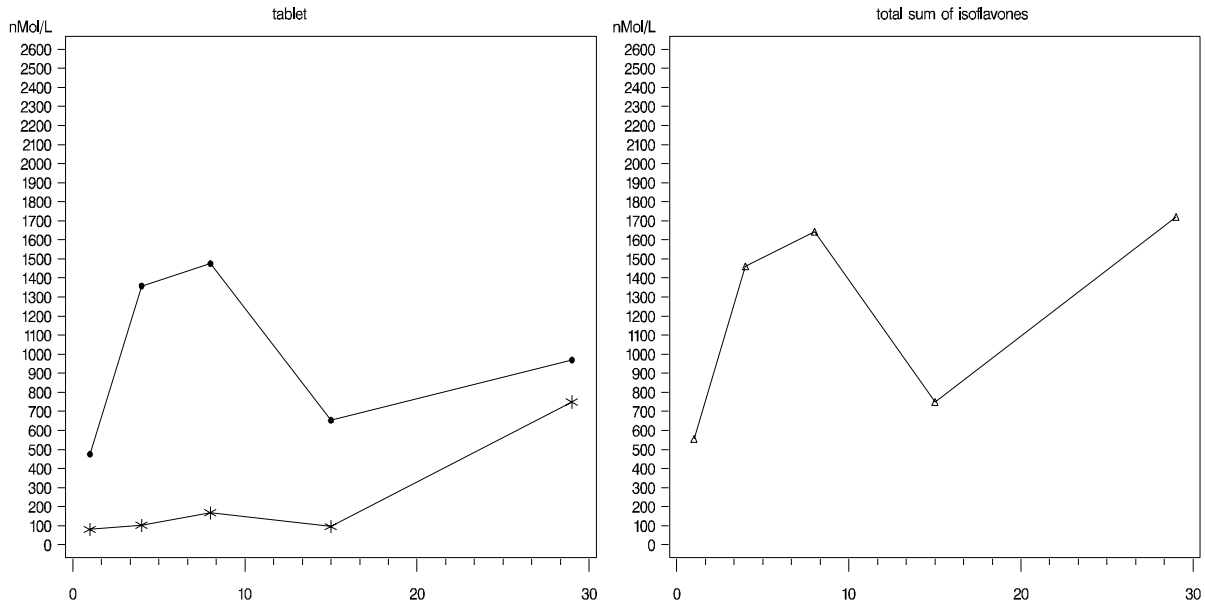
Figure A 2: Concentration-time profiles for residual concentration of daidzein, genistein, equol, and sum of all isoflavones for all study subjects (days 1, 3, 7, 14, 28 of period II).
Legend: * = daidzein, • = genistein, ◊ = equol, Δ = total sum of isoflavones.



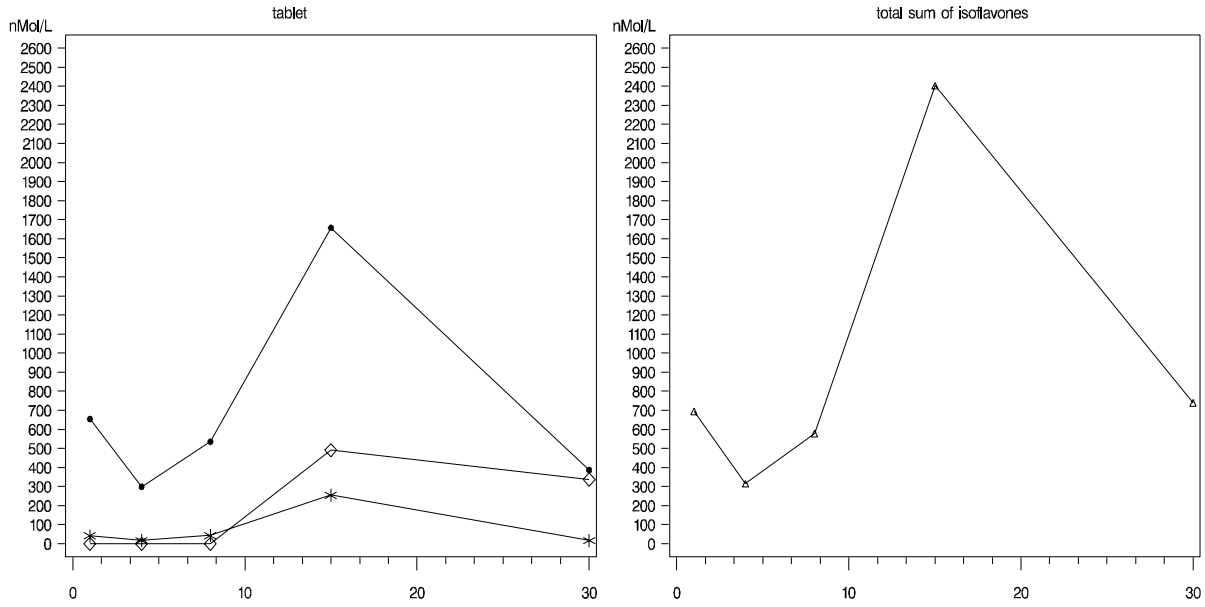
SNR 3


capsule
nMol/L
total sum of isoflavones
nMol/L

SNR 5

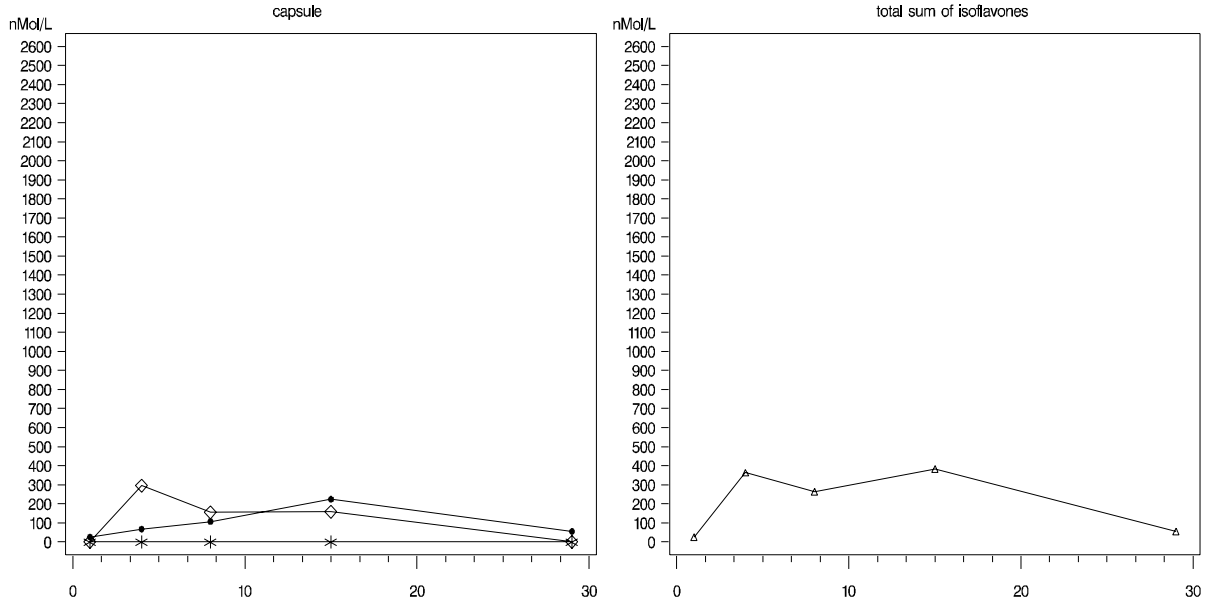

tablet
nMol/L
total sum of isoflavones
nMol/L

SNR 6


tablet
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

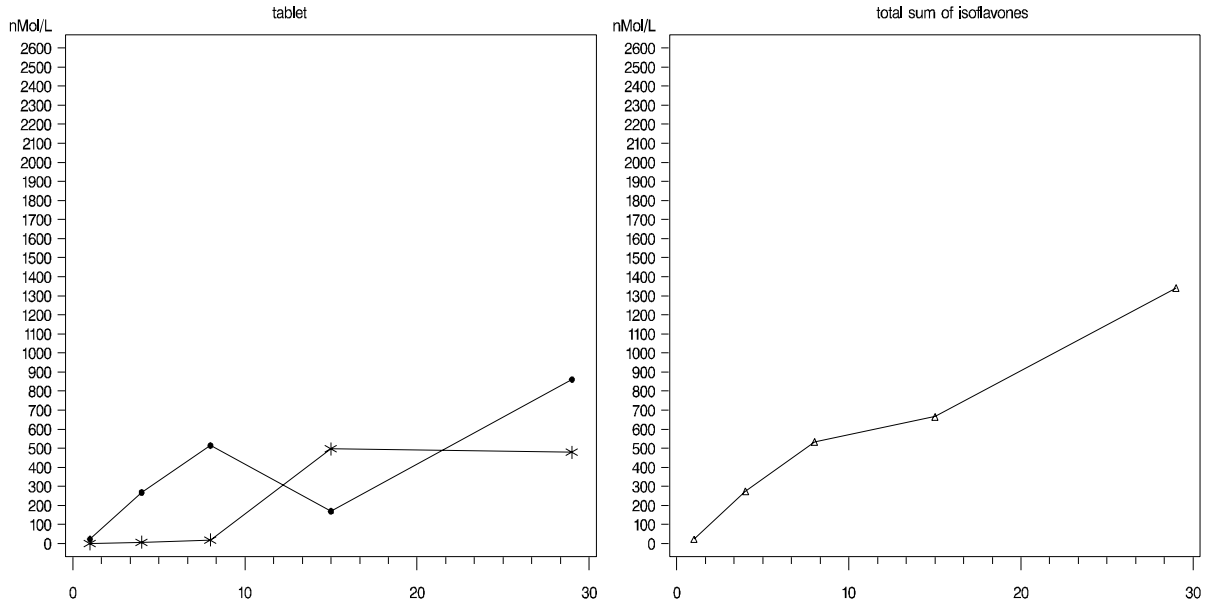
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

SNR 7


capsule
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

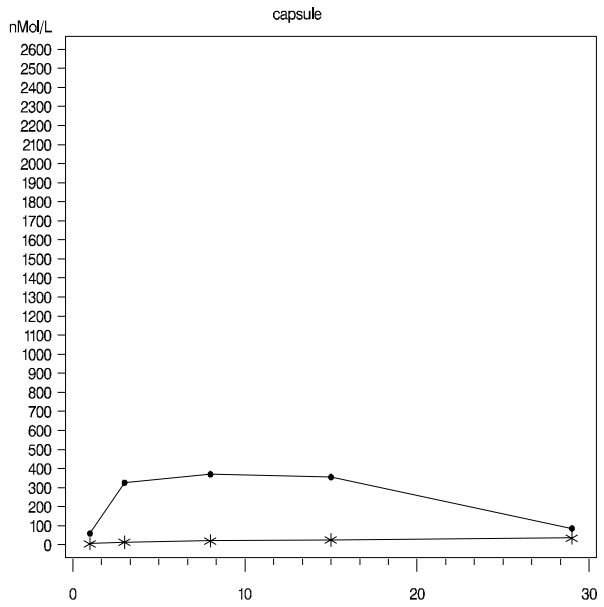
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

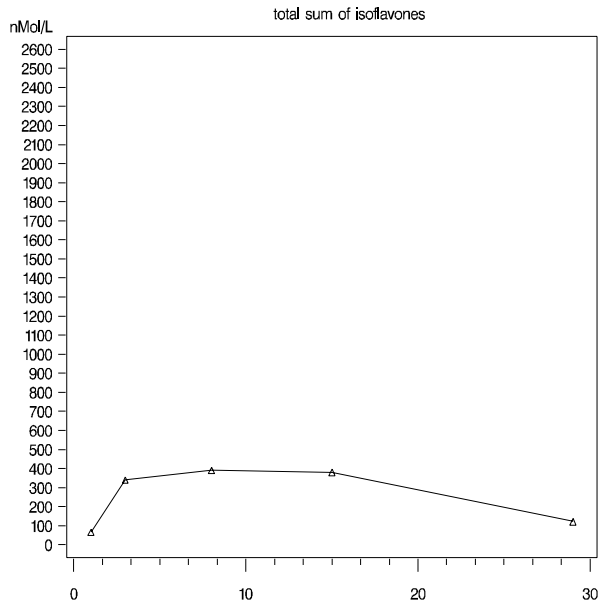
SNR 8

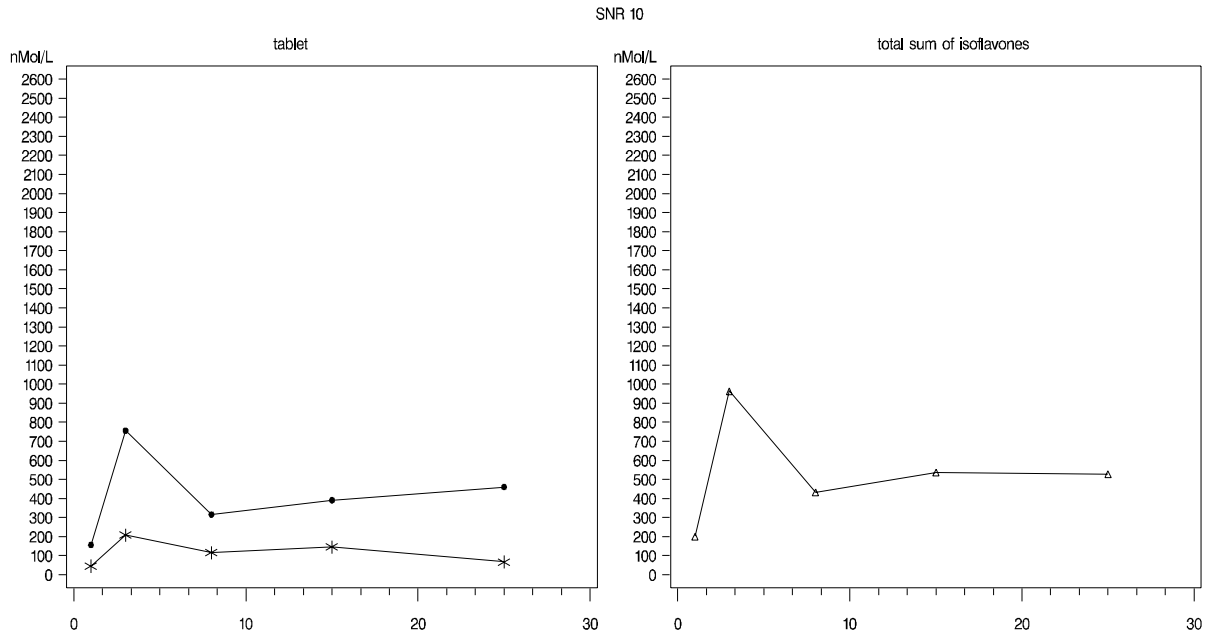

tablet
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

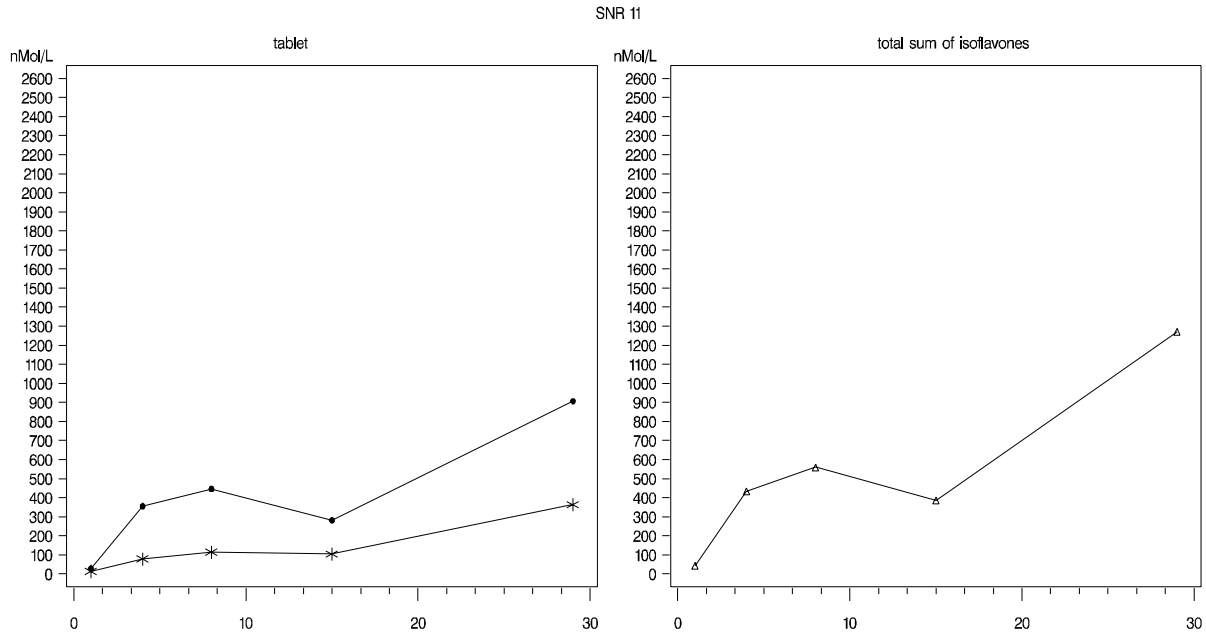
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

SNR 9

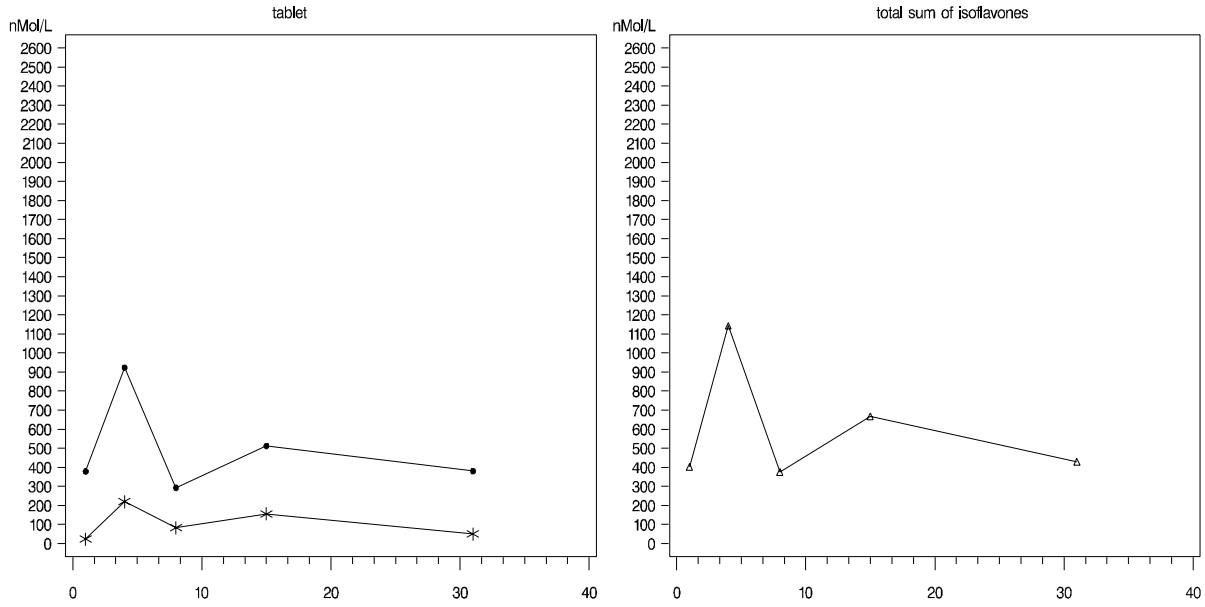

capsule
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30


total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30


SNR 10
tablet
nMol/L
total sum of isoflavones
nMol/L

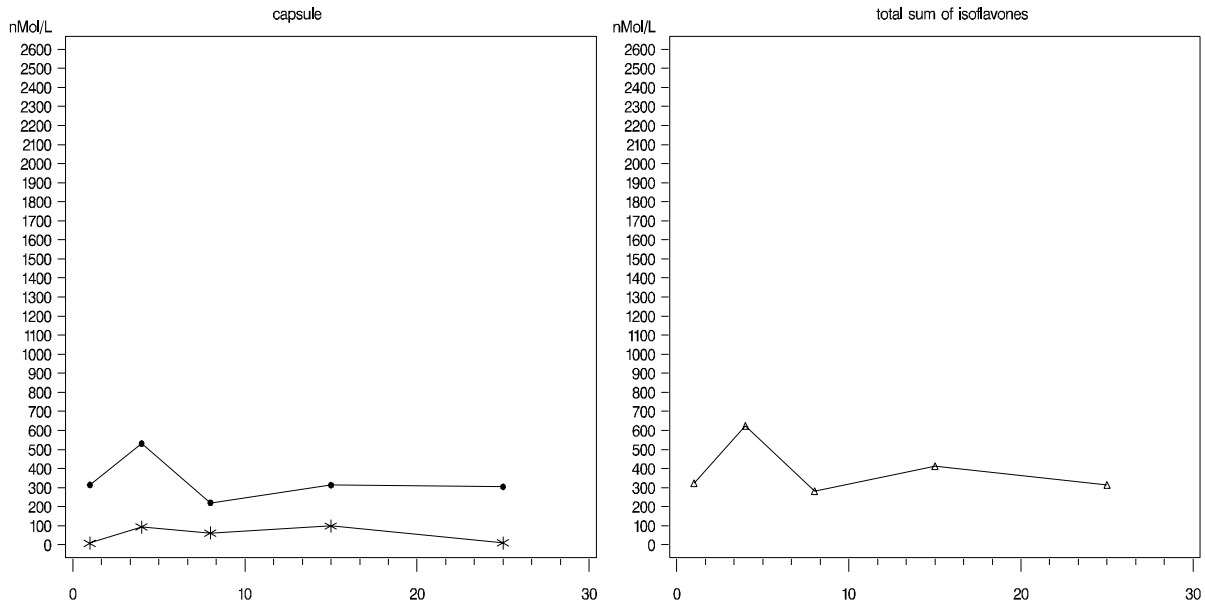

SNR 11
tablet
nMol/L
total sum of isoflavones
nMol/L

SNR 12


tablet
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40

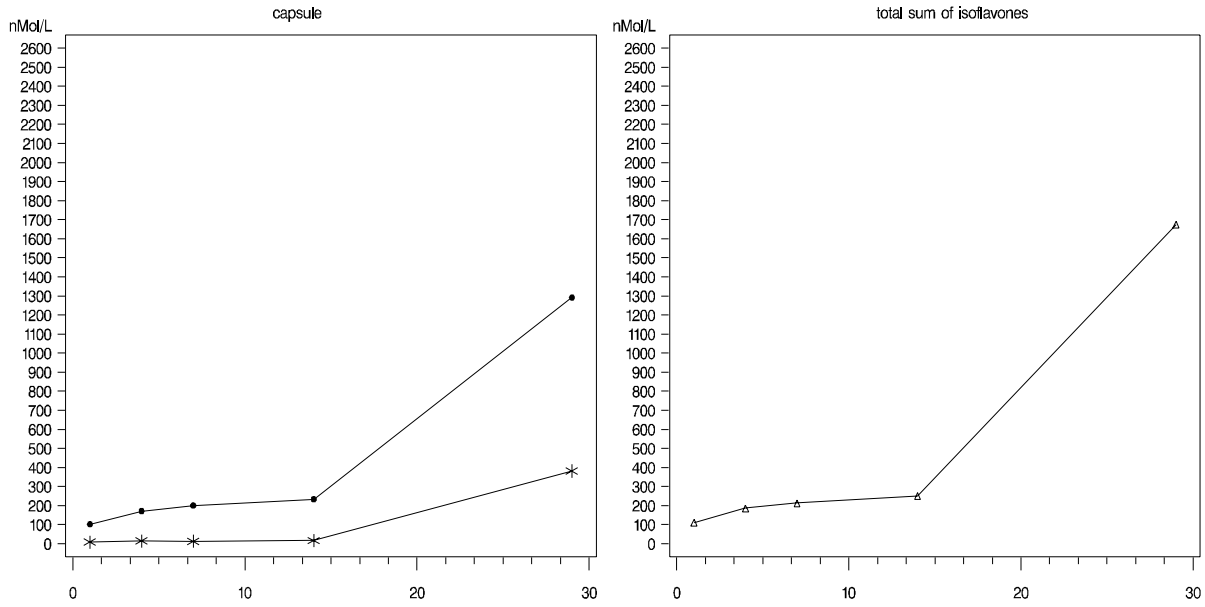
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40

SNR 13


capsule
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

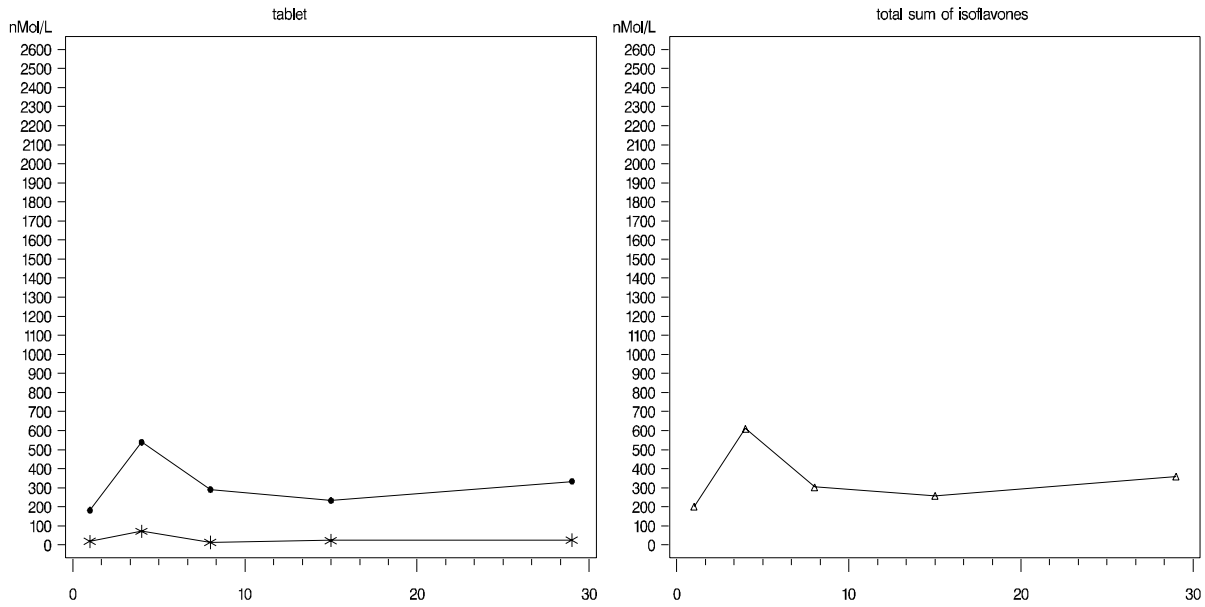
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

SNR 14


capsule
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

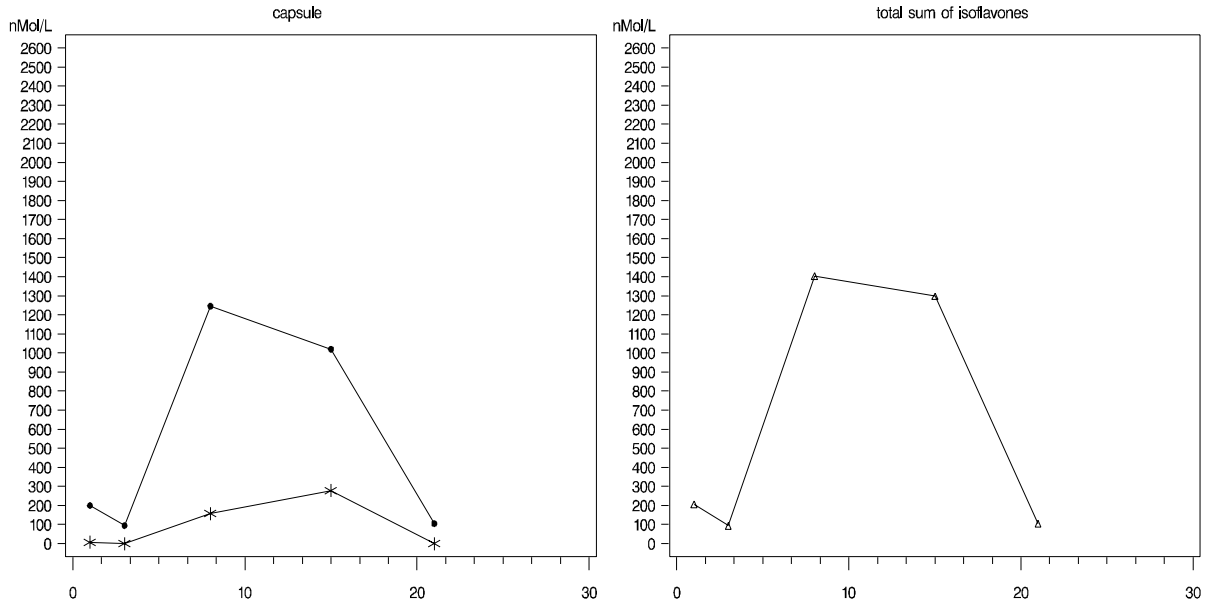
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

SNR 15


tablet
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

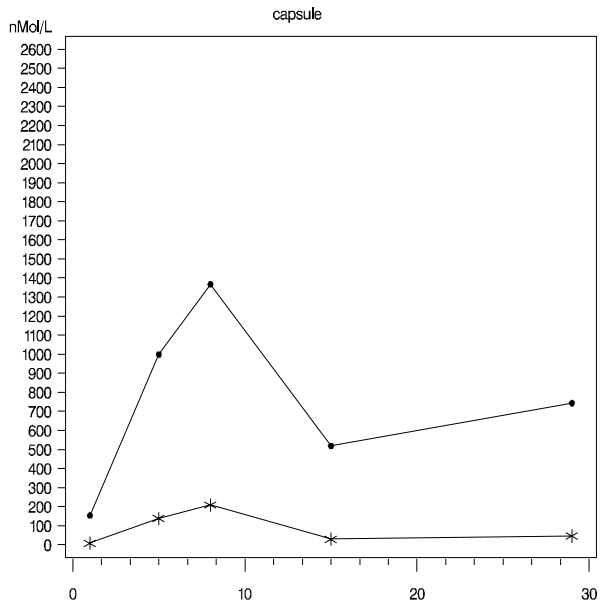
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

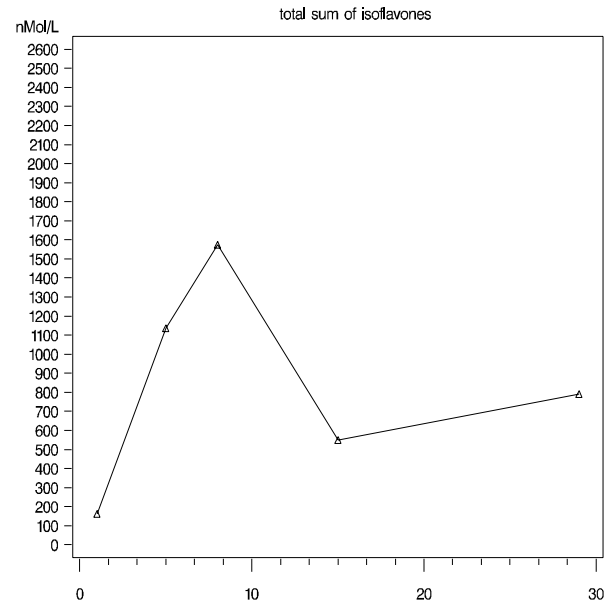
SNR 17


capsule
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

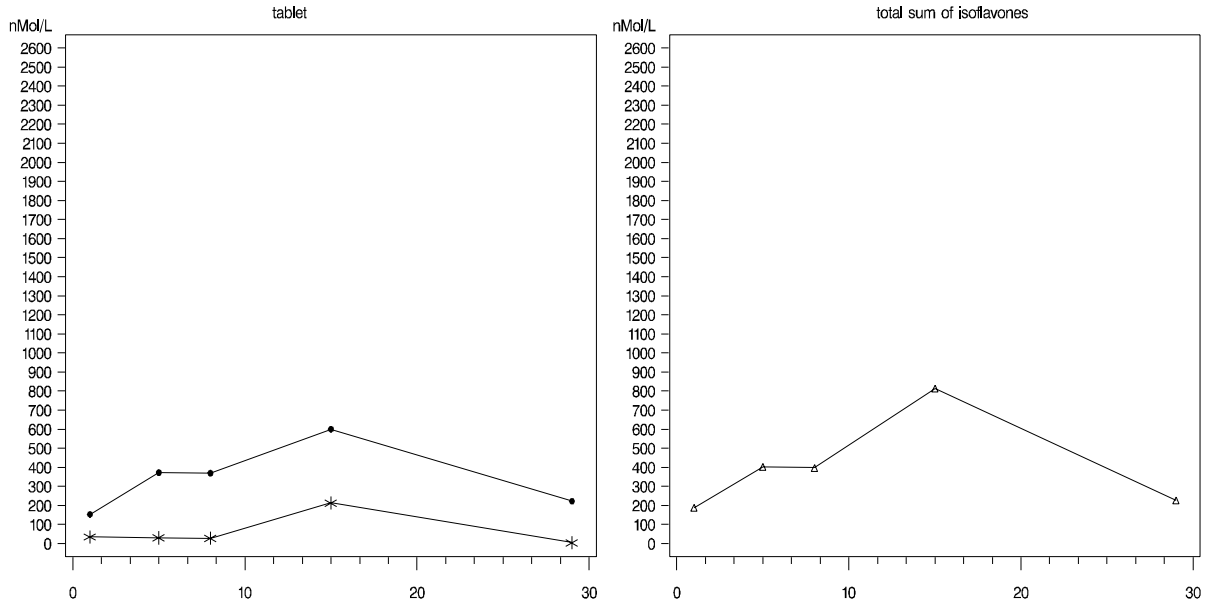
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

SNR 18


capsule
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

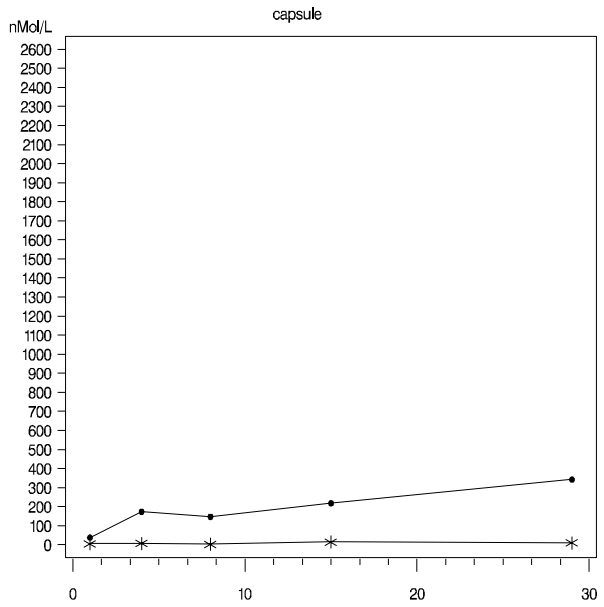

total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

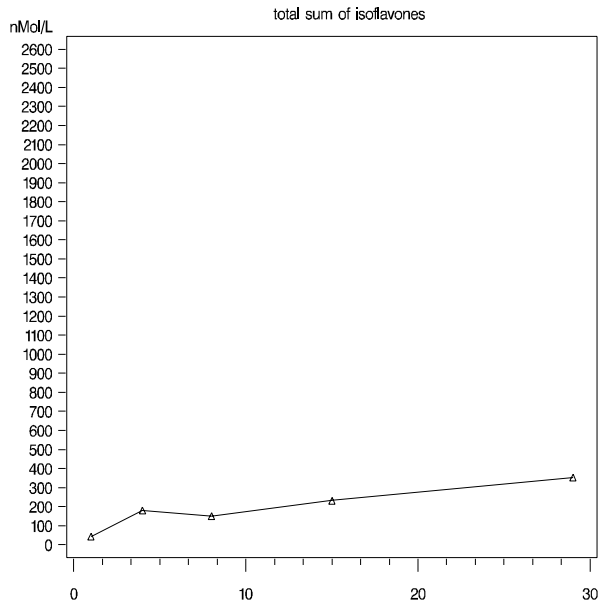
SNR 19


tablet
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

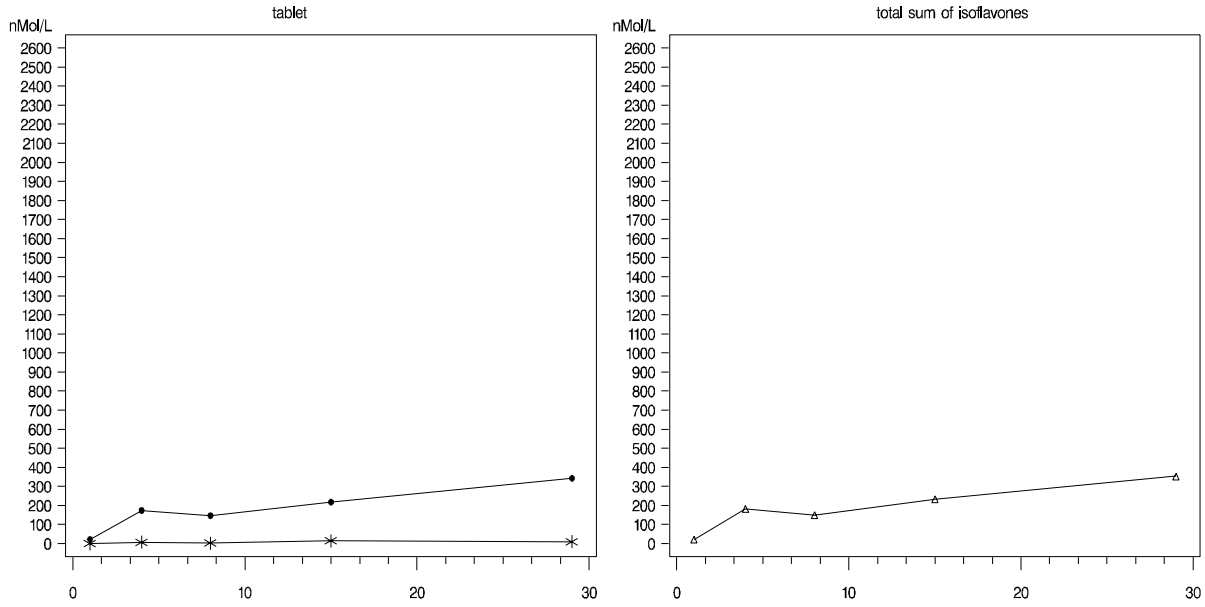
total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

SNR 20


capsule
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

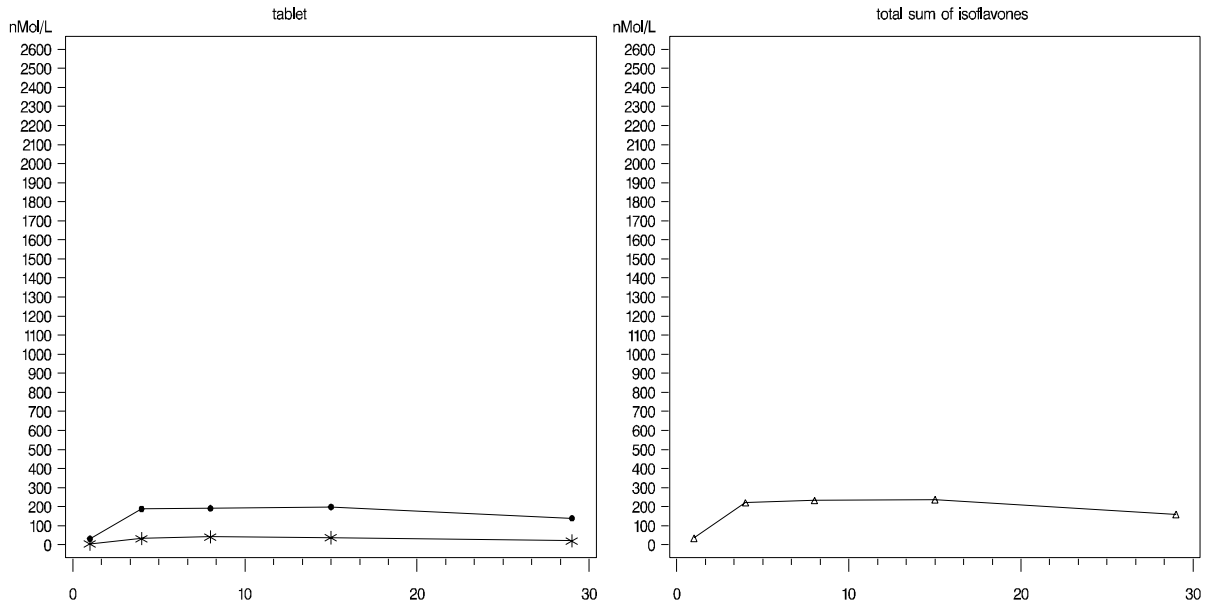

total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

SNR 21


tablet
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

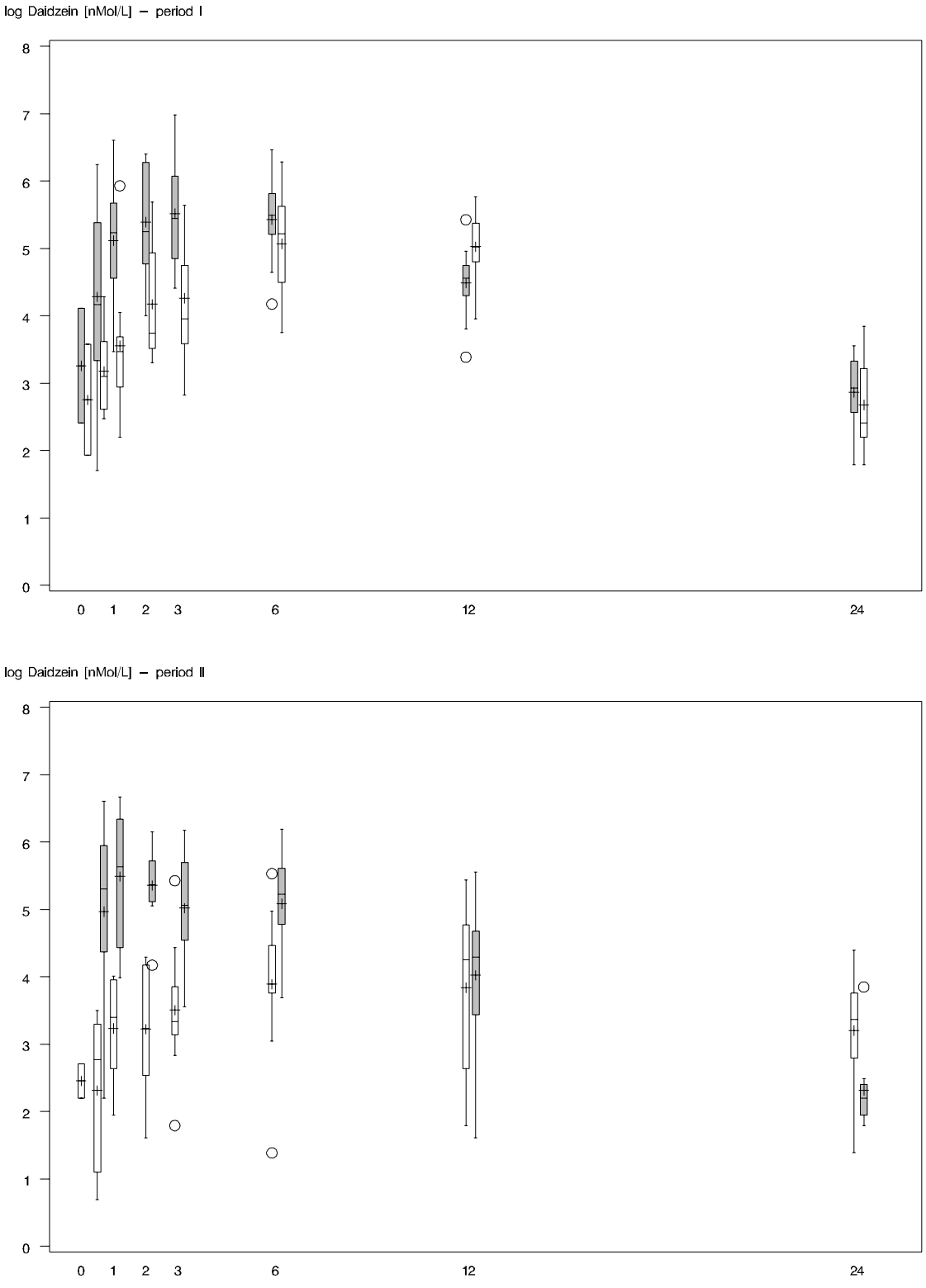
SNR 22


tablet
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

total sum of isoflavones
nMol/L
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30

Figure A 3: Capsule- and tablet formulation: box-plots of the log transformed values of daidzein in period I, day 1 of period II, and for the days 1, 3, 7, 14, and 28 of period II.

Legend: capsule formulation, tablet formulation



log Daidzein [nMol/L] – for days 1, 3, 7, 14 and 28 of period II

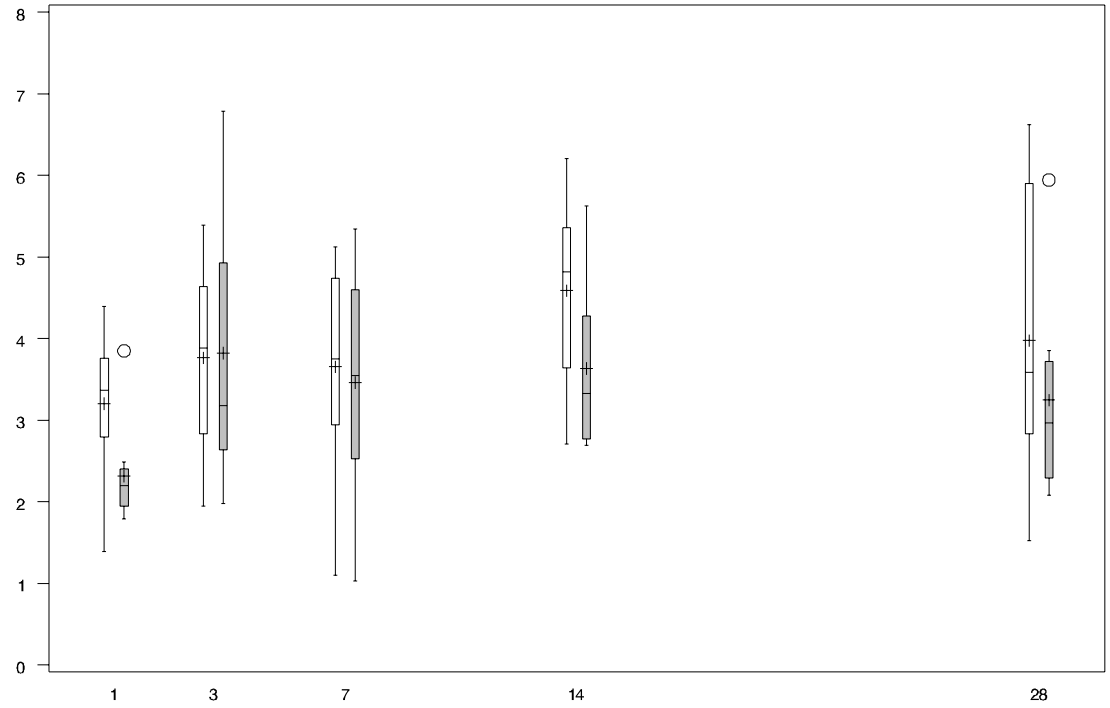
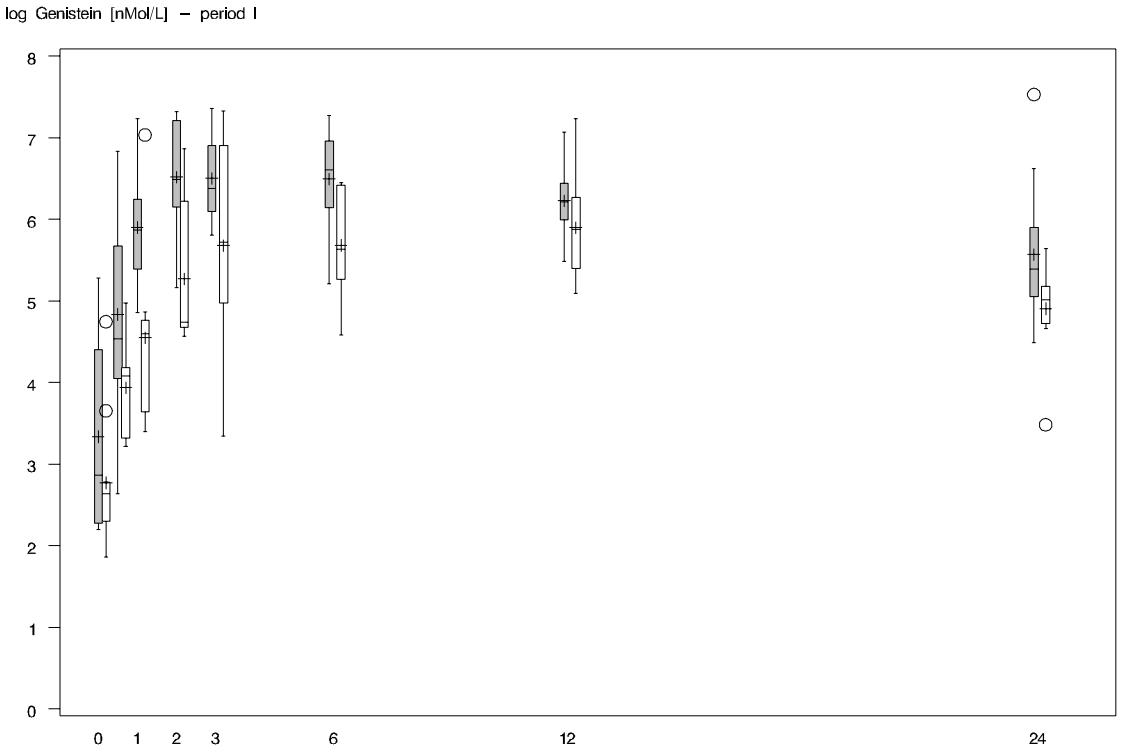
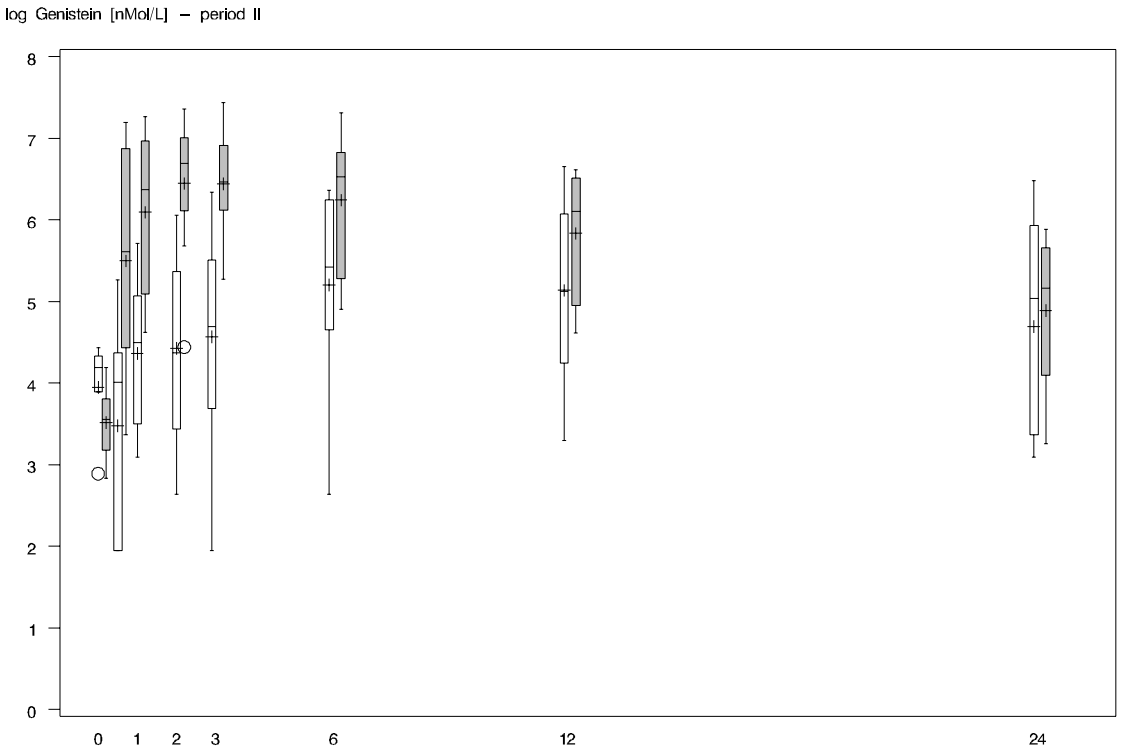


Figure A 4: Capsule- and tablet formulation: box-plots of the log transformed values of genistein in period I, day 1 of period II, and for the days 1, 3, 7, 14, and 28 of period II.

Legend: capsule formulation, tablet formulation





log Genistein [nMol/L] – for days 1, 3, 7, 14 and 28 of period II

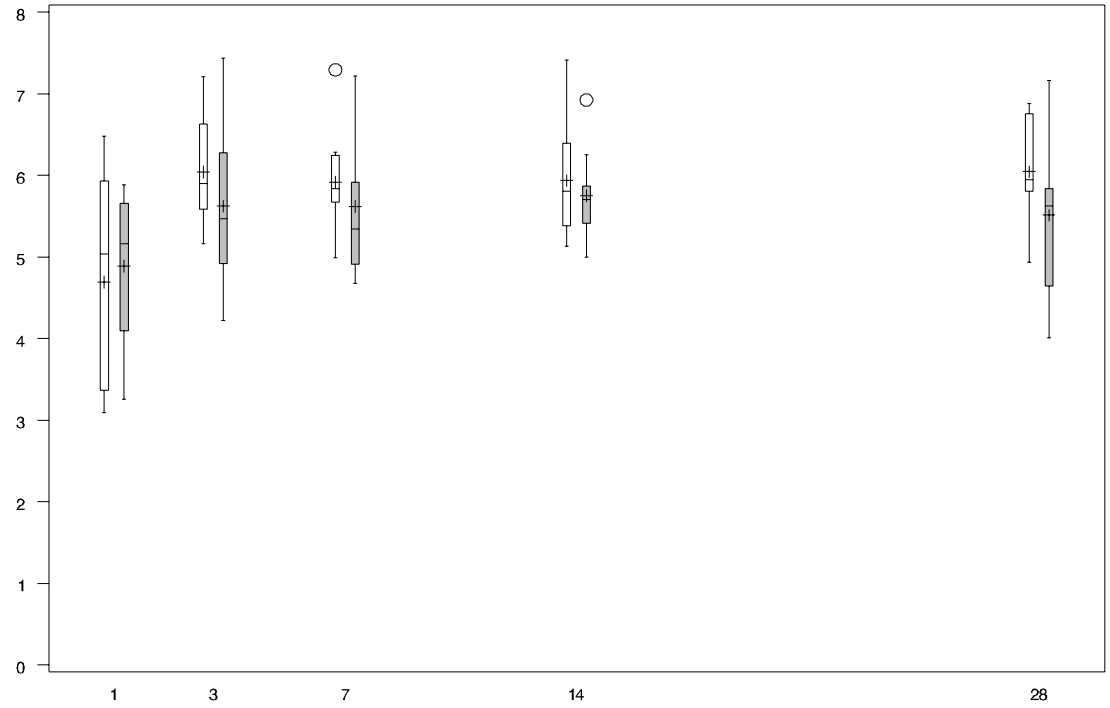
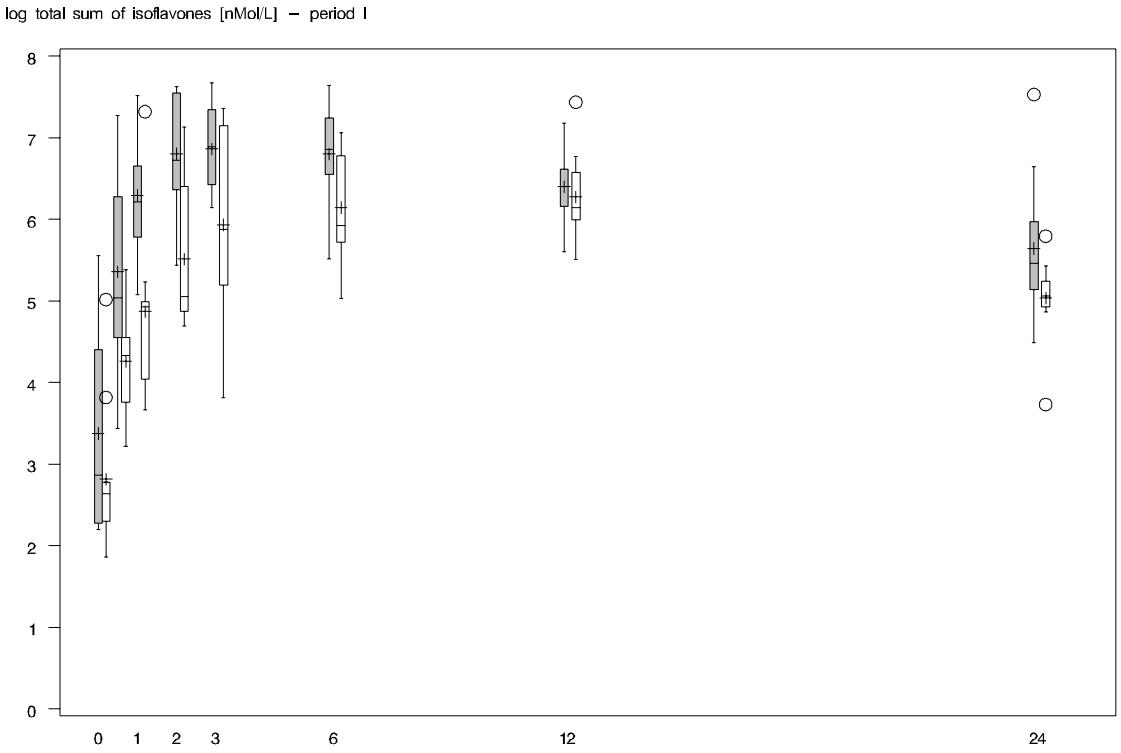
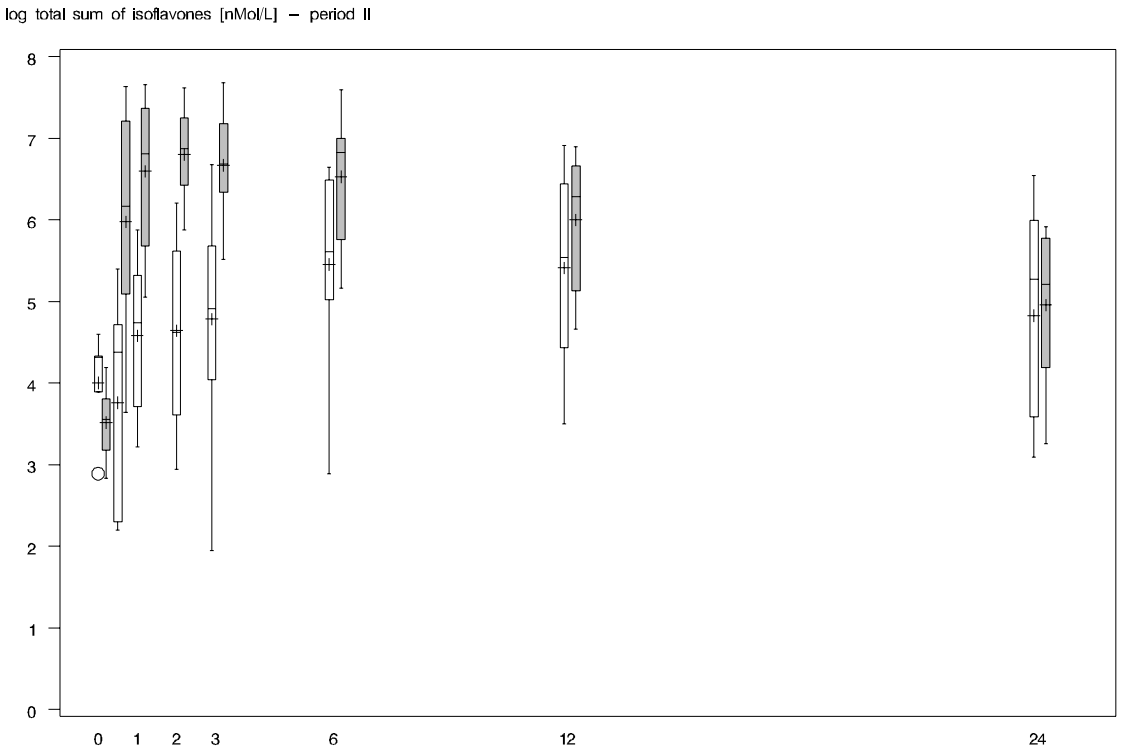


Figure A 5: Capsule- and tablet formulation: box-plots of the log transformed values of total sum of all isoflavones in period I, day 1 of period II, and for the days 1, 3, 7, 14, and 28 of period II.

Legend: capsule formulation, tablet formulation





log total sum of isoflavones [nMol/L] – for days 1, 3, 7, 14 and 28 of period II

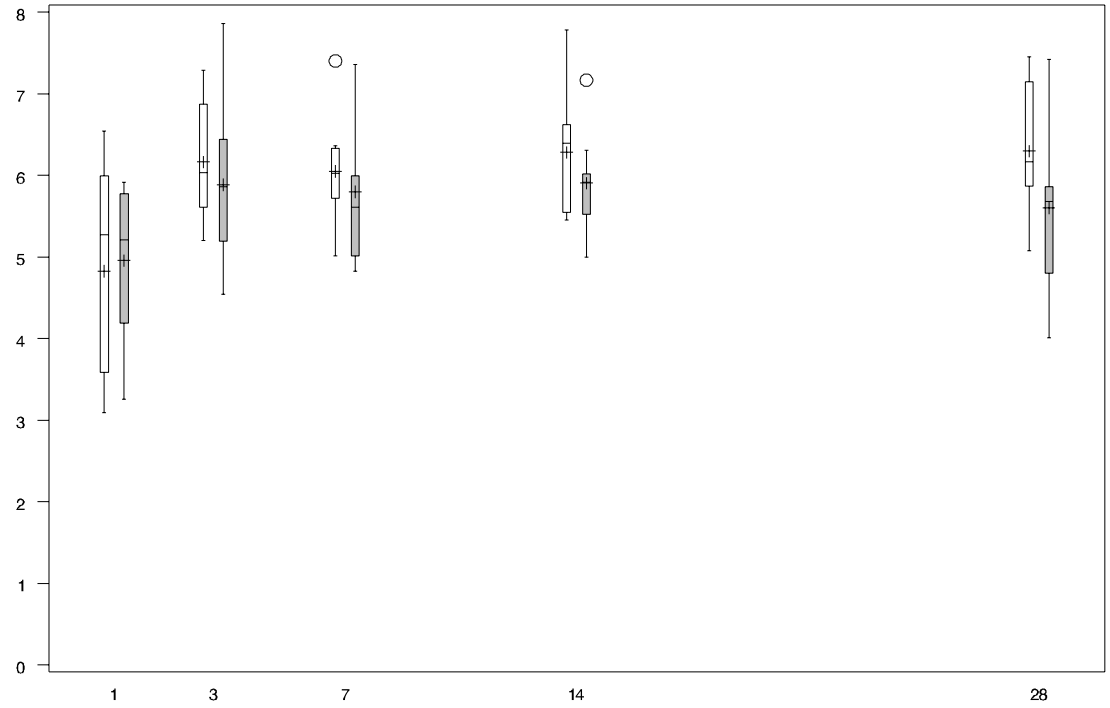
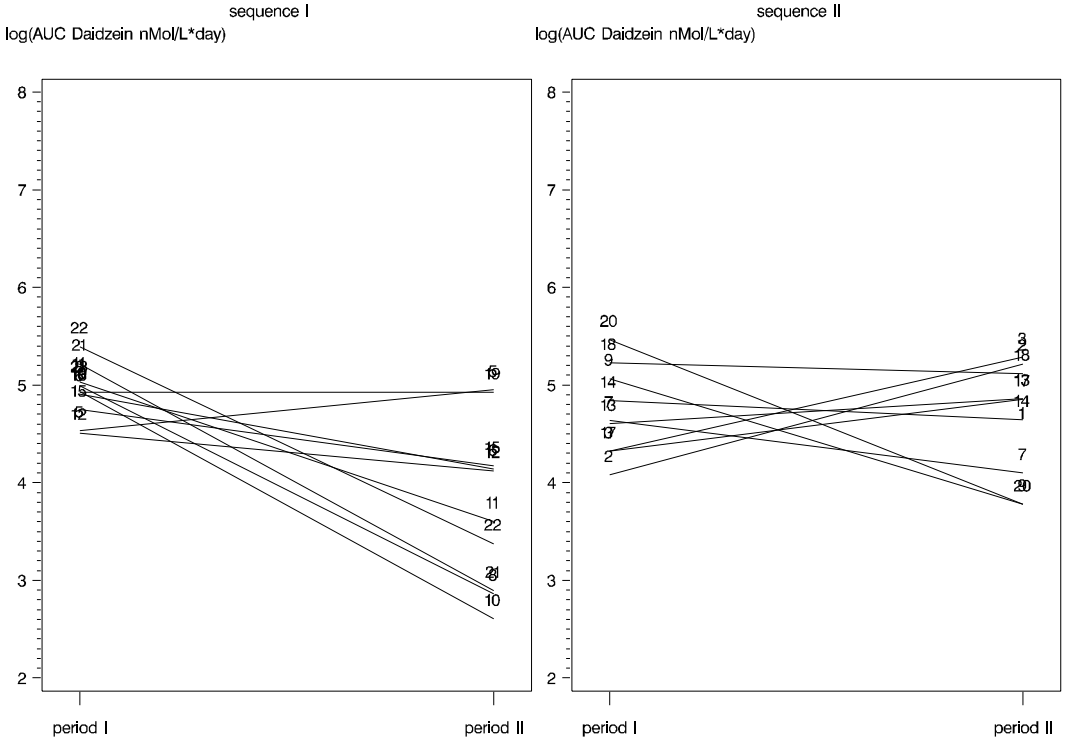
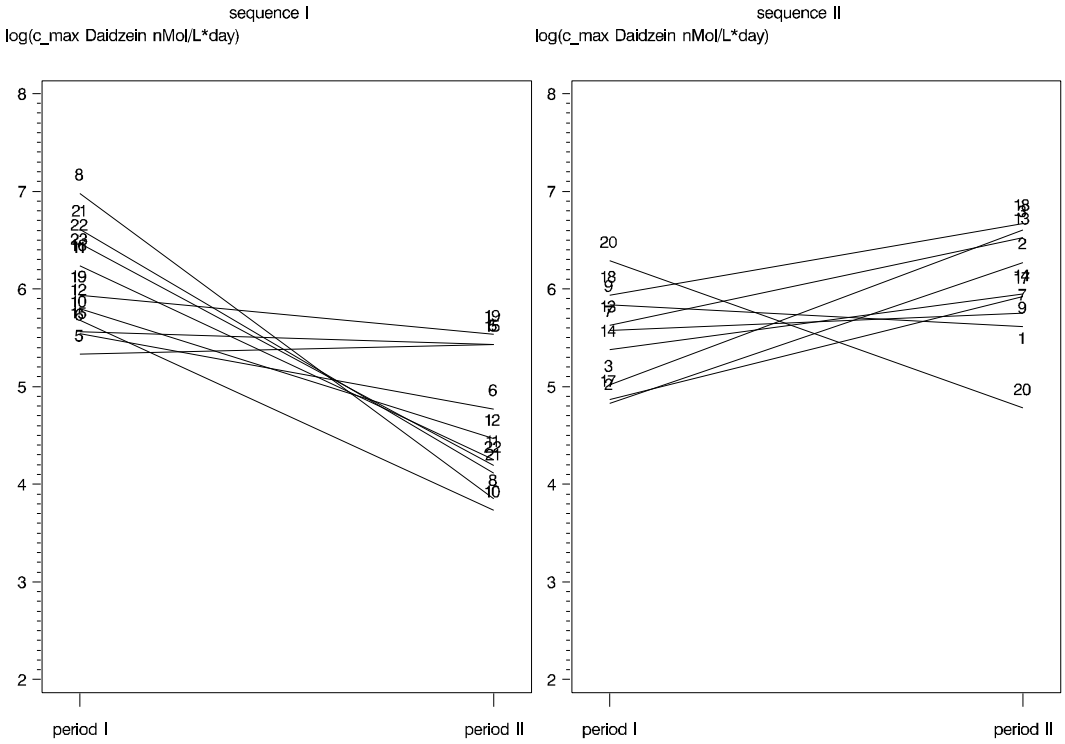
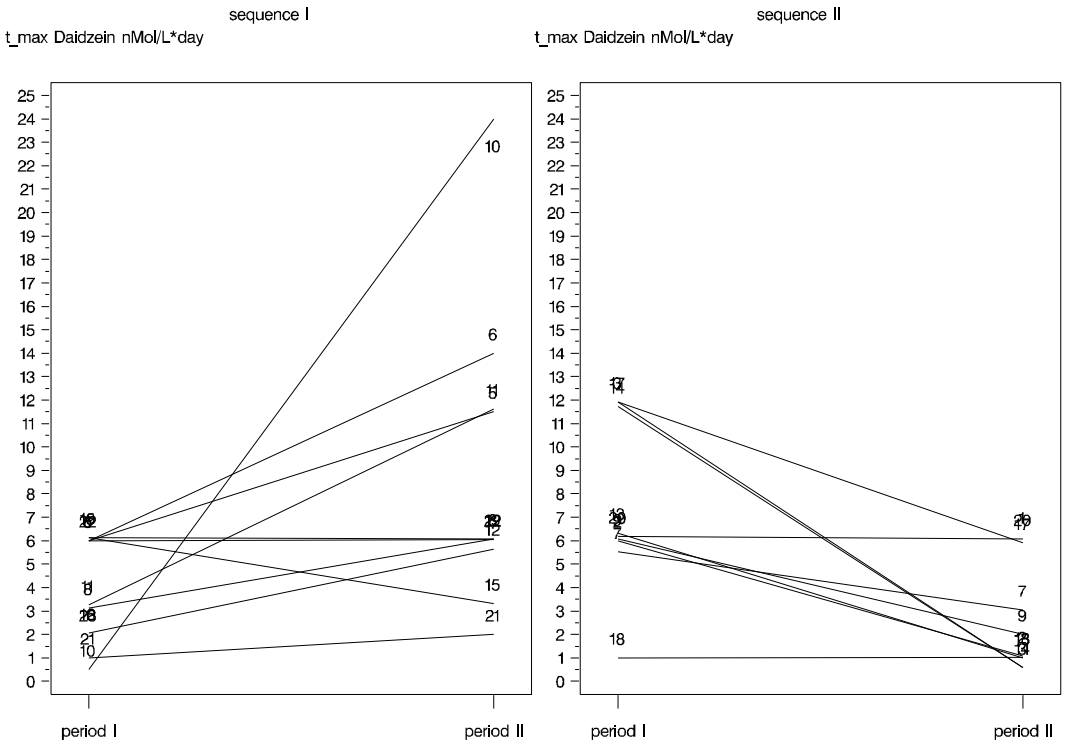


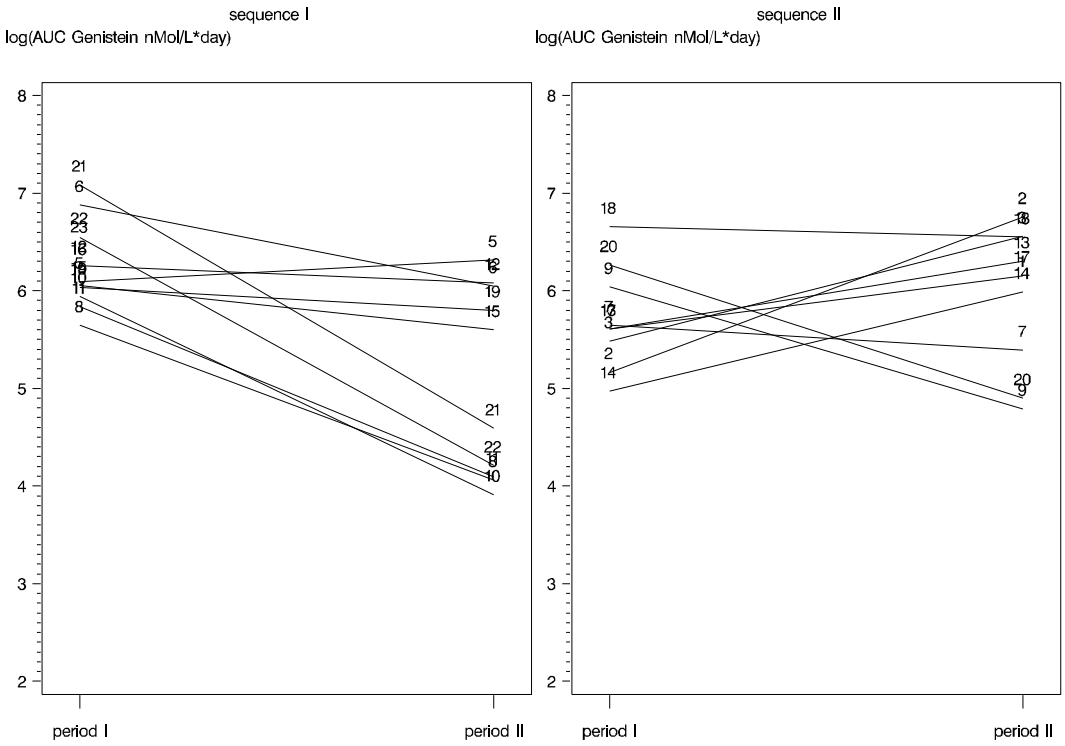
Figure A 6: Response-by-periods plots: subject profiles for log($AUC_{0\rightarrow 24}$), log($c\_max_{0\rightarrow 24}$), $t\_max_{0\rightarrow 24}$ for daidzein, genistein and sum of all isoflavones for both treatment sequences.

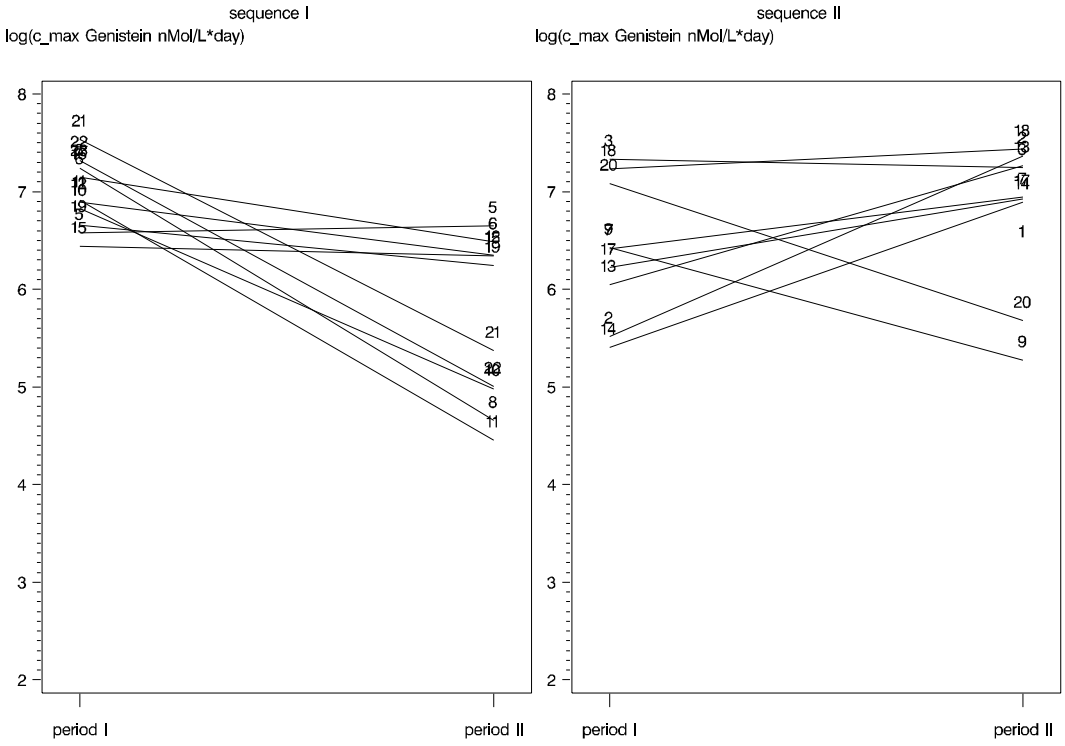
Legend: sequence I: period I: capsule, period II: tablet
sequence II: period I: tablet, period II: capsule

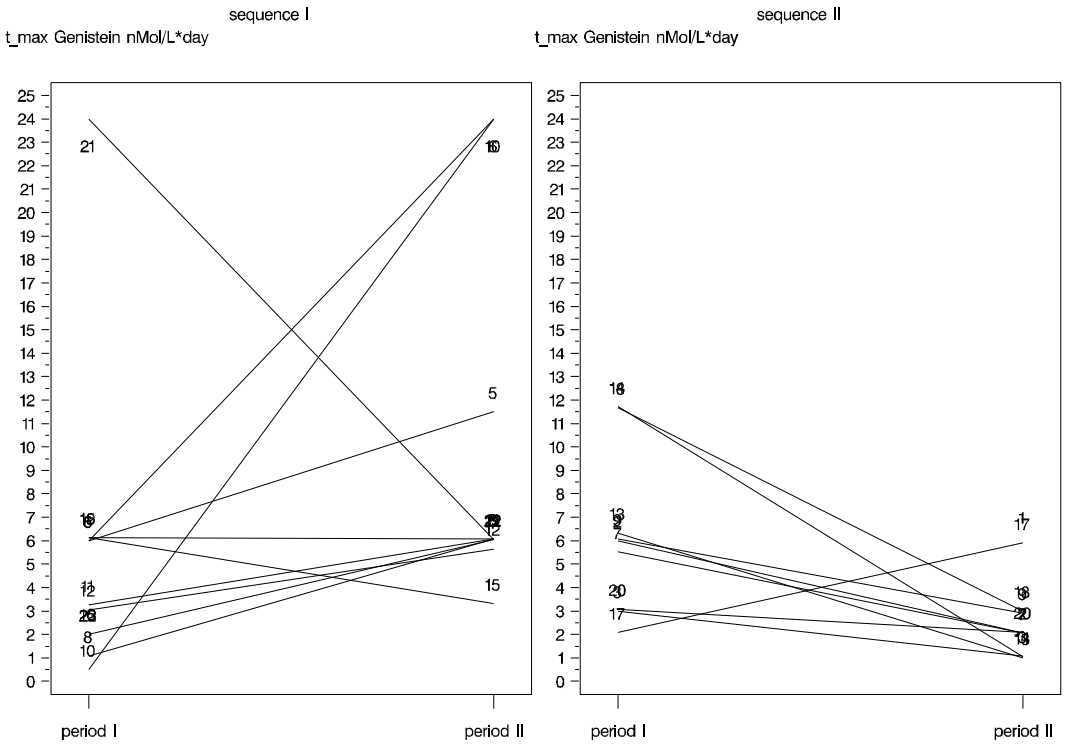


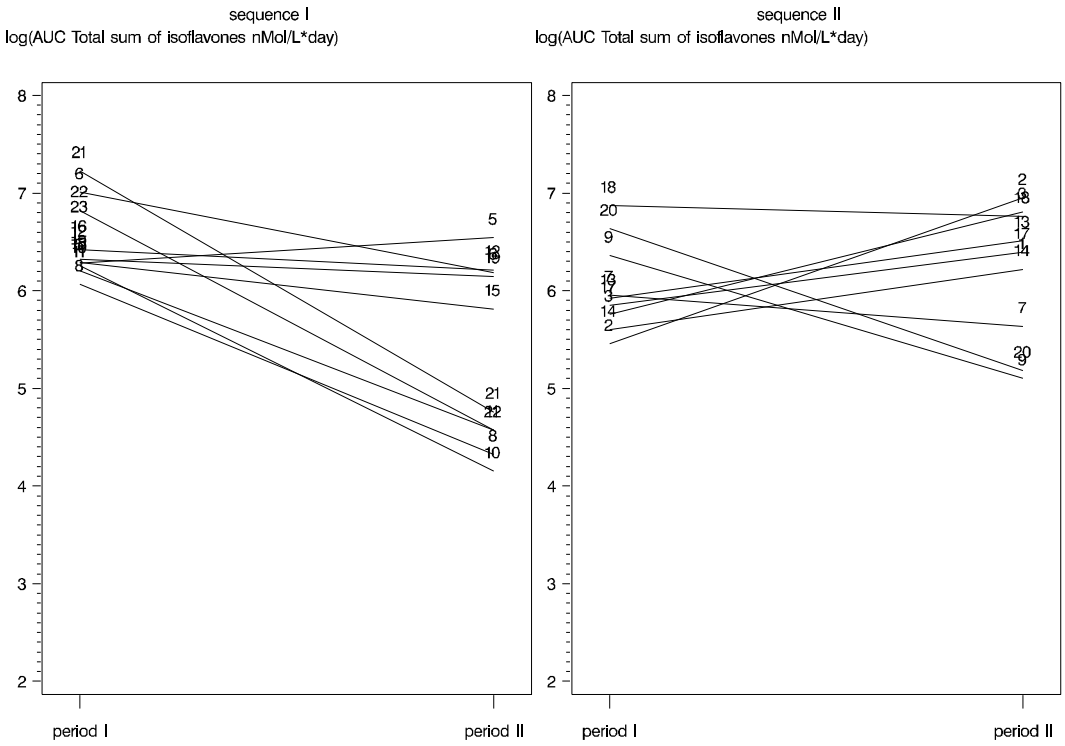


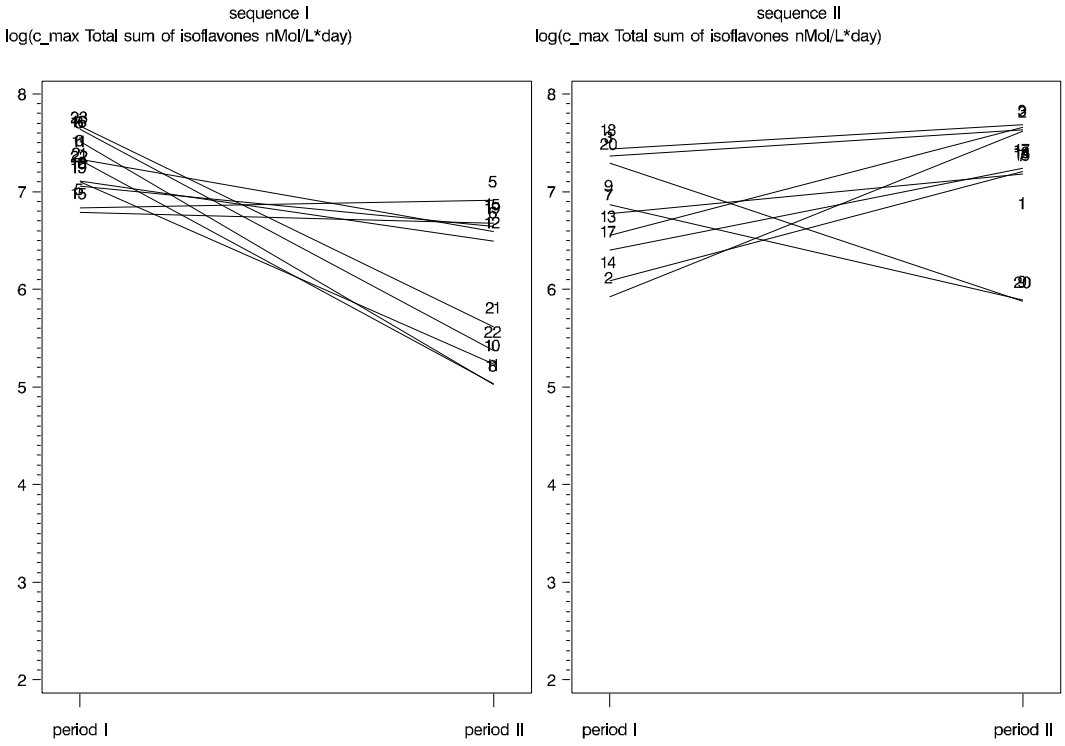

sequence I
t_max Daidzein nMol/L*day
sequence II
t_max Daidzein nMol/L*day
period I
period II
period I
period II


sequence I
log(AUC Genistein nMol/L*day)
sequence II
log(AUC Genistein nMol/L*day)
period I
period II
period I
period II


sequence I
log(c_max Genistein nMol/L*day)
sequence II
log(c_max Genistein nMol/L*day)
period I
period II
period I
period II


sequence I
t_max Genistein nMol/L*day
sequence II
t_max Genistein nMol/L*day
period I
period II
period I
period II


sequence I
log(AUC Total sum of isoflavones nMol/L*day)
sequence II
log(AUC Total sum of isoflavones nMol/L*day)
period I
period II
period I
period II


sequence I
log(c_max Total sum of isoflavones nMol/L*day)
sequence II
log(c_max Total sum of isoflavones nMol/L*day)
period I
period II
period I
period II

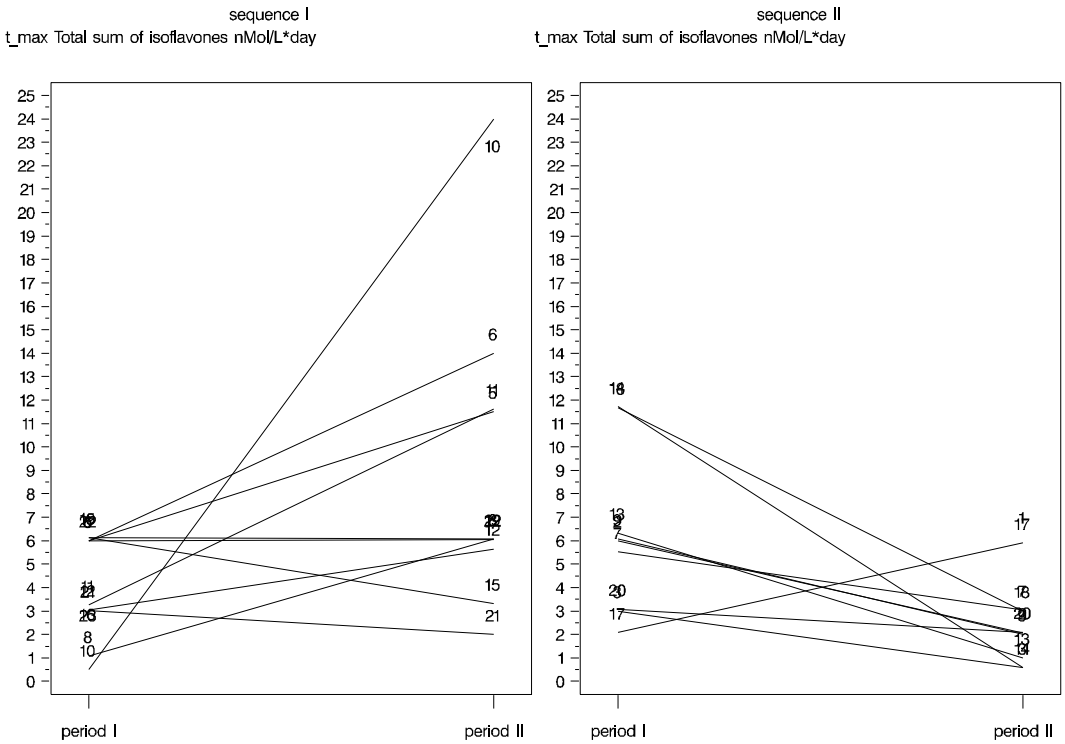
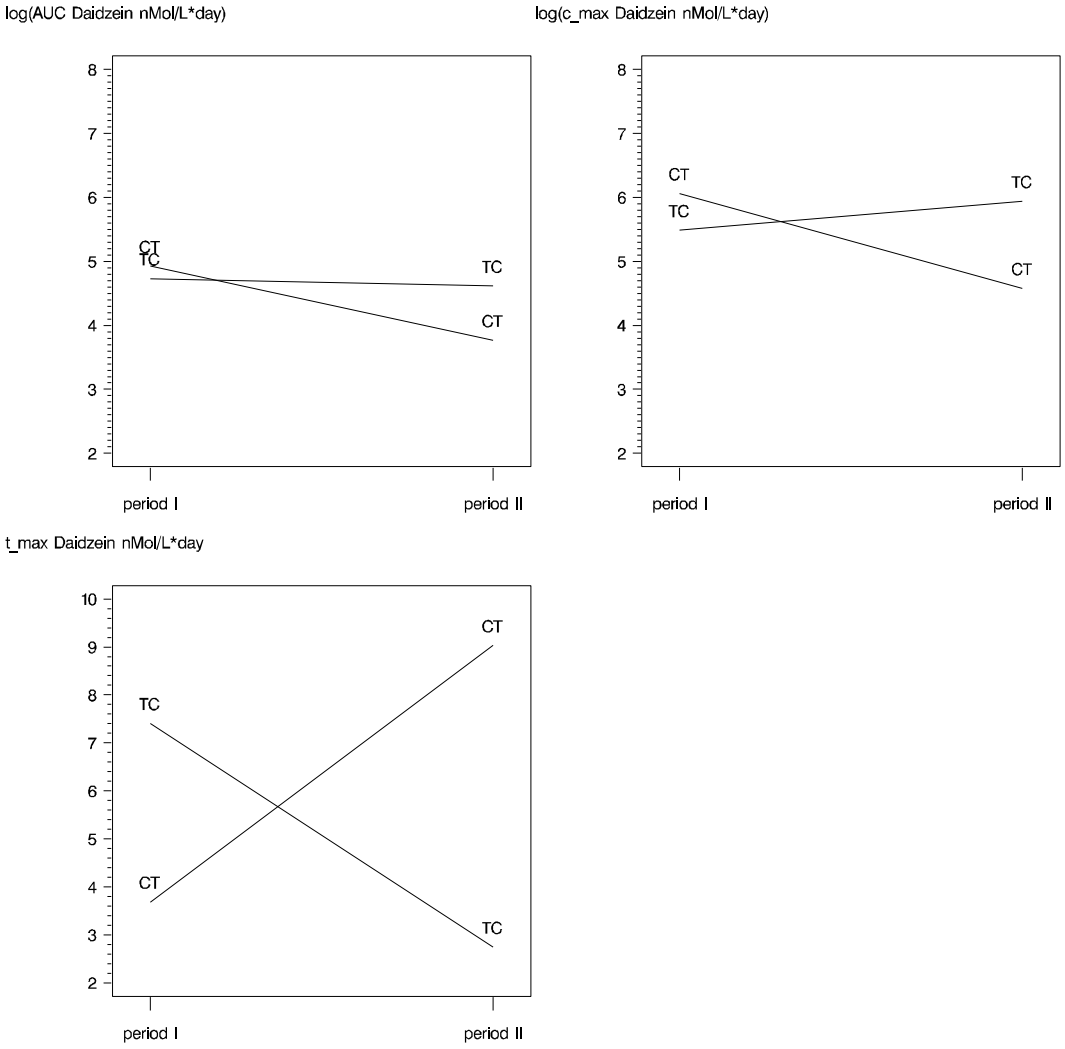
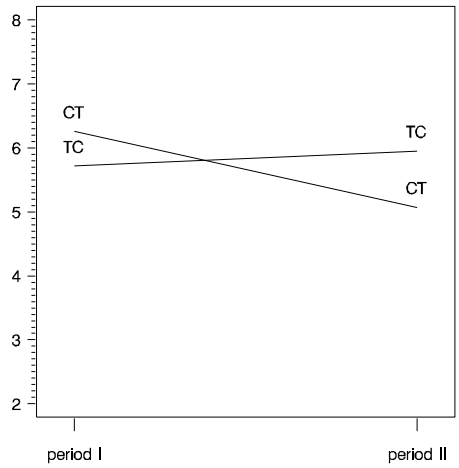

sequence I
t_max Total sum of isoflavones nMol/L*day
sequence II
t_max Total sum of isoflavones nMol/L*day
period I
period II
period I
period II

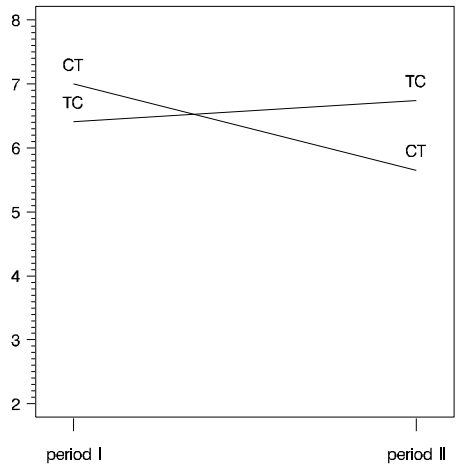
Figure A 7: Groups-by-periods plots: for log($AUC_{0\rightarrow 24}$), log($c\_max_{0\rightarrow 24}$), $t\_max_{0\rightarrow 24}$ for daidzein, genistein and sum of all isoflavones for both treatment sequences.



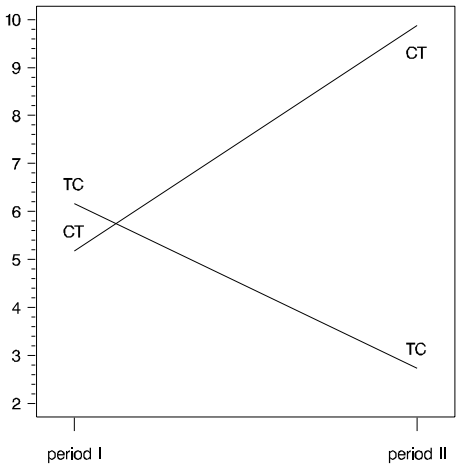
log(AUC Genistein nMol/L*day)



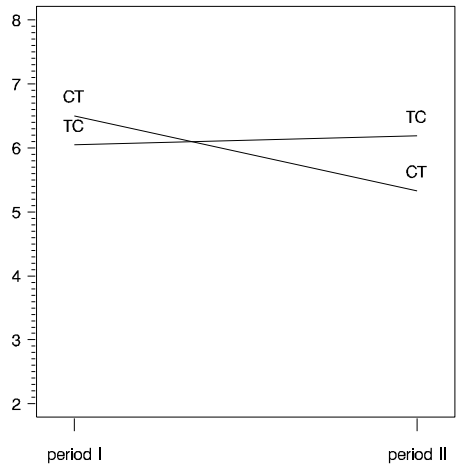
log(c_max Genistein nMol/L*day)



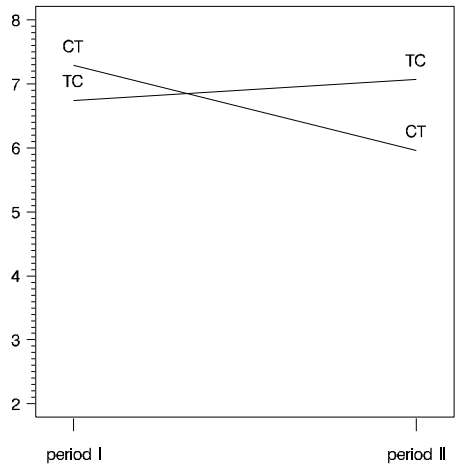
t_max Genistein nMol/L*day



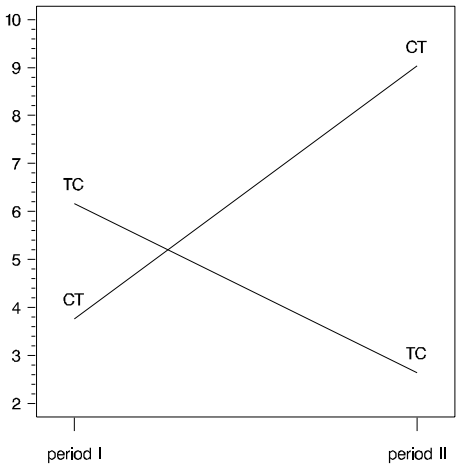
log(AUC Total sum of isoflavones nMol/L*day)



log(c_max Total sum of isoflavones nMol/L*day)



t_max Total sum of isoflavones nMol/L*day



Datum: _____ **Studien-Nr.:** _____

Anamnese zur allgemeinen Befindlichkeit

Patienteninitialen **Geburtsdatum** **Telefonnummern: Arbeit / Privat**

Sehr geehrte Frau _____!

Bei Ihrem ersten Besuch: Kreuzen Sie von den aufgelisteten Beschwerden bitte nur die an, die bei Ihnen in den letzten **4 Wochen** aufgetreten sind. Bei den folgenden Besuchen geben Sie die Beschwerden seit dem letzten Ausfüllen dieses Bogens an.
Wenn Sie keine Beschwerden in dem bezeichneten Organbereich haben, kreuzen Sie "nein" an und gehen zum nächsten Abschnitt.

Welche Beschwerden haben Sie?

1. Wie fühlen Sie sich insgesamt (Allgemeinbefinden)?

sehr schlecht	schlecht	mäßig	gut	sehr gut
☐	☐	☐	☐	☐

2. Wie fühlen Sie sich insgesamt seit Ihrem letzten Besuch?

viel schlechter	etwas schlechter	un-verändert	etwas besser	viel besser
☐	☐	☐	☐	☐

3. Herz-Kreislauf-Beschwerden (25)

☐nein ☐ja, welche?	gering (1)	leicht (2)	mittel (3)	stark (4)	sehr stark (5)
Schwindel (121)	☐	☐	☐	☐	☐
Herzstolpern (122)	☐	☐	☐	☐	☐
Herzjagen (123)	☐	☐	☐	☐	☐
Engegefühl in der Brust (124)	☐	☐	☐	☐	☐
Andere Herz-/ Kreislaufbeschwerden (125)	☐	☐	☐	☐	☐

welche?_____.

Score gesamt:

4. Beschwerden des Verdauungstrakts (115)

☐nein ☐ja, welche?	gering (1)	leicht (2)	mittel (3)	stark (4)	sehr stark (5)
Zungenbrennen (92)	☐	☐	☐	☐	☐
Völlegefühl (101)	☐	☐	☐	☐	☐
Blähungen (96)	☐	☐	☐	☐	☐
Durchfall (95)	☐	☐	☐	☐	☐
Verstopfung (97)	☐	☐	☐	☐	☐
Übelkeit (98)	☐	☐	☐	☐	☐
Erbrechen (99)	☐	☐	☐	☐	☐
Aufstoßen, Sodbrennen (100)	☐	☐	☐	☐	☐
Unverträglichkeit fetter Speisen (102)	☐	☐	☐	☐	☐
Oberbauchbeschwerden (103)	☐	☐	☐	☐	☐
Bauchkrämpfe (108)	☐	☐	☐	☐	☐
Appetitmangel (109)	☐	☐	☐	☐	☐
Heißhunger (110)	☐	☐	☐	☐	☐
Vermehrtes Durstgefühl (111)	☐	☐	☐	☐	☐
Alkohol-Unverträglichkeit (112)	☐	☐	☐	☐	☐
Andere Verdauungsbeschwerden (113)	☐	☐	☐	☐	☐

welche? _____.

Score gesamt:

4a: Wie oft haben Sie Stuhlgang?

___mal **pro Tag** od. ___ mal **pro Woche** od.___ mal **pro Monat**

Datum _____ **Studien-Nr.:** _____

5. Beschwerden des Bewegungsapparates (40)

☐ nein ☐ ja, welche?	gering (1)	leicht (2)	mittel (3)	stark (4)	sehr stark (5)
Ziehen oder Schmerzen in den großen Gelenken (151)	☐	☐	☐	☐	☐
Ziehen oder Schmerzen in den kleinen Gelenken (152)	☐	☐	☐	☐	☐
Schwellungen von Gelenken (153)	☐	☐	☐	☐	☐
Ziehen oder Schmerzen in den Muskeln (154)	☐	☐	☐	☐	☐
Muskelkrämpfe (66)	☐	☐	☐	☐	☐
Muskelschwäche	☐	☐	☐	☐	☐
Schmerzen / Verspannungen im Nacken / Schulterbereich (156)	☐	☐	☐	☐	☐
Rücken-/ Kreuzschmerzen (157)	☐	☐	☐	☐	☐
Andere Gelenk-/ Muskelbeschwerden (158)	☐	☐	☐	☐	☐

welche? _____.

Score gesamt:

6. Beeinträchtigung des Allgemeinbefindens (105)

☐ nein ☐ ja, welche?	gering (1)	leicht (2)	mittel (3)	stark (4)	sehr stark (5)
Leistungsminderung (161)	☐	☐	☐	☐	☐
Aufgeregtheit, innere Unruhe (162)	☐	☐	☐	☐	☐
chronische Müdigkeit (163)	☐	☐	☐	☐	☐
Einschlafstörung (165)	☐	☐	☐	☐	☐
Durchschlafstörung (166)	☐	☐	☐	☐	☐
Kopfschmerz, Migräne (172)	☐	☐	☐	☐	☐
Frieren (173)	☐	☐	☐	☐	☐
Hitzewallungen (174)	☐	☐	☐	☐	☐
Nächtliches Schwitzen (175)	☐	☐	☐	☐	☐
Schweißausbrüche, tagsüber und nachts (176)	☐	☐	☐	☐	☐
Gewichtszunahme (177)	☐	☐	☐	☐	☐
Gewichtsabnahme (178)	☐	☐	☐	☐	☐
Wassereinlagerungen (179)	☐	☐	☐	☐	☐
Infektanfälligkeit (181)	☐	☐	☐	☐	☐

Score gesamt:

7. Beschwerden der Harnwege (20)

☐ nein ☐ ja, welche?	gering (1)	leicht (2)	mittel (3)	stark (4)	sehr stark (5)

welche? _____.

Score gesamt:

8. Spezifische Fragen für Frauen, mit oder ohne Periode, falls zutreffend

☐ nein ☐ ja, welche?	gering (1)	leicht (2)	mittel (3)	stark (4)	sehr stark (5)
Rückenschmerzen oder Ziehen im Unterbauch (1)	☐	☐	☐	☐	☐
Blähbauch oder Völlegefühl (2)	☐	☐	☐	☐	☐
Niedergeschlagenheit (3)	☐	☐	☐	☐	☐
Migräneartiger Kopfschmerz (5)	☐	☐	☐	☐	☐
Zyklusabhängige Gewichtszunahme (6)	☐	☐	☐	☐	☐
Morgendliche Schwellung von Händen und/oder Füßen (7)	☐	☐	☐	☐	☐
Brustschmerzen (Spannen, Ziehen) (9)	☐	☐	☐	☐	☐
Schmerzen-vor d. Periode (11)	☐	☐	☐	☐	☐
- während d. Periode (12)	☐	☐	☐	☐	☐
Andere Beschwerden vor oder während der Periode? (13)	☐	☐	☐	☐	☐

welche? _____.

Score gesamt:

8a: Letzte Periode am: ____. ____. ____

Erklärung der Probandin:

☐ Diesen Fragebogen habe ich vollständig durchgelesen und die Fragen sorgfältig beantwortet

☐ Ich wünsche noch Informationen zu folgenden Punkten:

Anmerkungen des Arztes:

Ort/Uhrzeit Unterschrift der Probandin

Unterschrift der Ärztin/ des Arztes

Signatures

Heidelberg, 15.02.2006 Dr. Jens Dreyhaupt

Heidelberg, 15.02.2006 Dr. Katrin Jensen

Heidelberg, 15.02.2006 Christina Klose