## APPENDIX 2 - PROTOCOL SUMMARY - Study H3S-MC-GGGK 36-Month Data

## ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

### Study
### H3S-MC-GGGK
### 36-Month Data

**Study Title (Study No.):** Raloxifene Hydrochloride and Placebo in the Treatment of Postmenopausal Women with Osteoporosis: Population Analyses (H3S-MC-GGGK, 36-Month Data)

**Investigator(s)/Center(s):** GGGK was a multicenter study. 181 principal investigators in 25 countries.

**Study Period:** The clinical phase corresponding to the 36-month analysis for Study GGGK was December 1994 through September 1998.

**Objectives:** Use population analysis to 1) characterize the pharmacokinetics of raloxifene; identify patient factors and laboratory parameters that may influence raloxifene disposition in patients with osteoporosis, 2) evaluate the pharmacodynamics of total lumbar spine BMD, femoral neck BMD, and serum osteocalcin; evaluate dose and steady-state raloxifene concentration effect on total lumbar spine and femoral neck BMD; identify patient factors that may influence pharmacodynamic endpoints; 3) identify potential relationships between steady-state plasma raloxifene concentrations and patient discontinuations, statistically significant treatment-emergent adverse events, serious adverse events, and concomitant medication use.

**Study Design:** Single blood samples were obtained from raloxifene-treated patients following 3, 6, 12, 18, 24, and 36 months of treatment. Pharmacokinetic sampling was limited to 17 of the 181 principal investigators and included investigators in five countries (US, UK, Argentina, Netherlands, and Norway).

**Subjects:** Population pharmacokinetic evaluation included data from 1712 postmenopausal women whose age ranged from 45 to 81 years.

**Criteria for Inclusion:** The clinical trial consisted of two parallel substudies in separate populations. Substudy I included postmenopausal women with low BMD measurements ‹ 2.5 standard deviations or more below normal peak bone loss for healthy, premenopausal women. Substudy II included postmenopausal women with at least one prevalent vertebral fracture in addition to the above criteria.

**Test Product, Dose and Mode of Administration, Batch and Formulation No.:** One or two 60-mg raloxifene HCl tablets administered orally, once-daily; [redacted] Batch and formulation numbers are compiled in NDA Section 6.

**Reference Therapy, Dose and Mode of Administration, Batch and Formulation No:**
There were no pharmacokinetic or pharmacodynamic evaluations of patients randomly assigned to placebo.

**Duration of Treatment:** The double-blind treatment phase was 36 months.

**Analytical Method(s)/Validation(s)/Analytical Center(s)/Dates of Analysis:**

**Analytical Method Validation Analytical Center Dates of Analyses**

| Analytical Method | Validation | Analytical Center | Dates Analyses |
|---|---|---|---|
| Raloxifene: [redacted] | Range: 0.050 to 5.000 ng/mL linear<br>CV and RE ‹ 10% | Lilly Laboratory for Bioanalytical Research in Toronto, Canada | 24 August 1995 to 15 September 1998 |
| [redacted] | Range: 10.0 to 1000 ng/mL<br>Linear<br>CV and RE <10% | [redacted] | 13 July 1995 to 5 September 1998 |

**Methods**: **Pharmacokinetics:** A 0-24 month interim dataset was randomly divided into two datasets comprising ¾ (model development, index dataset) and ¼ (validation dataset) of the patients. The validated population pharmacokinetic model was used to evaluate concentrations during 24-36 months of raloxifene treatment. A one-compartment model with first-order appearance (Ka) and first-order elimination, parameterized in terms of total systemic clearance (CL) and apparent volume of distribution (V) was selected to describe the pharmacokinetics of raloxifene following oral administration. Patient factors being considered as potential covariates for the pharmacokinetic analyses were first evaluated using a generalized additive model. The predictive ability of the final population pharmacokinetic model was assessed using goodness-of-fit plots and quantitative assessment of prediction errors. The assessment of prediction errors included the mean prediction error (MPE), mean-squared prediction error (MSPE), and the magnitude of bias (MRE). An empirical Bayesian estimate of clearance obtained for each patient was used to calculate a 24-hour average concentration at steady state ($C_{ss,8}$). The population pharmacokinetic model developed and validated using the 0-24 month data was used to evaluate the 24-36 month concentration data. No modeling of the 0-36 month total raloxifene in hydrolyzed plasma (TRHP) data was performed.

**Pharmacodynamics:** Pharmacodynamic models were developed to describe the 0-36 month data for total lumbar spine BMD, femoral neck BMD and serum osteocalcin. A final placebo-progression model, including covariates, was developed to describe the time course of bone loss in the presence of calcium and vitamin D supplements and absence of raloxifene treatment. A raloxifene-response model was then developed consisting of the final placebo-progression model and a raloxifene-response function characterizing the change in BMD or osteocalcin attributable to raloxifene treatment alone. The change in BMD and osteocalcin over time was evaluated using linear and exponential models, as well as a B-spline representation. Greater than 80 factors were available for consideration as potential covariates (estrogen-responsive parameters were excluded) and approximately 50 were tested in the analysis. These covariates were first evaluated using a correlation analysis followed by a generalized additive model (GAM) and bootstrap iteration. The final placebo-progression model was incorporated into the raloxifene-response model as a baseline function. The effect of dose and raloxifene concentration on change was also evaluated.

**Patient Discontinuations, Adverse Events, and Concomitant Medication Evaluation:** Steady-state plasma raloxifene concentrations in patients who discontinued the study prior to 36 months, or in patients with statistically significant (overall incidence of at least 1% in the pooled raloxifene groups and a higher incidence rate in the raloxifene treatment groups compared to the placebo group) treatment-emergent adverse events or serious adverse events were evaluated to identify potential relationships between raloxifene concentrations and these events. In addition, plasma raloxifene concentrations in patients taking concomitant medications were evaluated to identify the effect of concomitant medications on plasma raloxifene concentrations. The analysis dataset contained 9637 raloxifene concentration records from 1774 patients of which 9069 concentration records from 1722 patients were quantifiable. A treatment-emergent adverse event (or serious adverse event) was considered to be temporally associated with a raloxifene concentration if the event occurred within 1 week before or after the plasma sample. A concomitant medication record was considered to be temporally associated with a raloxifene concentration if the concomitant medication was taken within 1 week prior to the plasma sample. Statistical analysis of patient discontinuation data was performed using a two-way mixed-effects analysis of variance (ANOVA) technique. The effect of raloxifene concentrations on the occurrence of adverse events was evaluated using logistic regression. The effects of concomitant medication on raloxifene concentrations were evaluated by a two-way mixed-effects ANOVA analysis on log-transformed concentration data. A statistically significant result was not considered clinically relevant unless the effect on plasma raloxifene concentration was greater than within-patient variability estimated by the population pharmacokinetic model.

**Results**:

**Population Pharmacokinetics:** The population pharmacokinetic evaluation included data from 1712 postmenopausal women whose age ranged from 45 to 81 years at study entry and who weighed between 33 and 133 kg. The majority of the samples (~60%) were obtained within 24 hours of the last administered dose. The overall observed mean steady-state raloxifene concentrations were 1.09 ng/mL and 2.05 ng/mL for 60- and 120-mg raloxifene HCl doses, respectively. The overall mean steady-state TRHP concentrations were 188.0 ng/mL and 323.5 ng/mL for 60- and 120-mg raloxifene HCl doses,

respectively. In this final population pharmacokinetic model, the population estimate (standard error of estimation expressed as percent or %SEE), of raloxifene CL and V was 55.1 L/hr (13.3 %SEE) and 2520 L (5.6 %SEE), respectively. The between-patient variability in CL and V were 39.4% (5.2 %SEE) and 77.5% (14.6 %SEE), respectively. The residual error was 30.9% (3.0 %SEE). Covariates identified as influencing clearance in the final population model were age at entry, estimated creatinine clearance normalized for lean body mass (CGLF) and smoking status. However, the effects of these covariates are less than the within-subject variability and are, therefore, not clinically relevant. A small MPE for both the index and validation datasets (0.137 versus 0.082 ng/mL) indicated an appropriate model. Similar results were observed for MRE between the 24-36 month and 0-24 month data. These results support the predictive ability of the final population pharmacokinetic model for raloxifene.

**Population Pharmacodynamics:** The placebo-progression model describing the change in total lumbar spine BMD during placebo administration indicated that the mean change in total lumbar spine BMD over the 36-month study period was insignificant. Patients randomly assigned to placebo treatment benefited from calcium and vitamin D supplementation and those with a lower BMI lost bone more rapidly. The raloxifene-response model indicated that raloxifene increased total lumbar spine BMD relative to placebo over the 36-month treatment period. The therapeutic effect of raloxifene was greater in patients with lower baseline BMD, higher osteocalcin concentration at study entry, and the most significant disease (Substudy II). The placebo-progression model describing the change in femoral neck BMD indicated that postmenopausal women lost bone over the 36-month study period. Patients with a low BMI, lower creatinine clearance, and higher baseline femoral neck BMD lost bone more rapidly. The raloxifene-response model for femoral neck BMD indicated that raloxifene increased BMD relative to placebo over the 36-month treatment period. The therapeutic effect of raloxifene was greater in patients with higher baseline osteocalcin concentration. The placebo-progression model for change in osteocalcin was influenced by calcium and vitamin D supplements, the baseline value of type I collagen fragment to creatinine ratio and creatinine clearance. The raloxifene-response model for osteocalcin indicated that raloxifene decreased overall bone turnover which resulted in a decrease in serum osteocalcin concentration relative to placebo. Patients responding better to raloxifene were those with greater time since menopause, higher baseline total alkaline phosphatase concentrations, and higher baseline serum osteocalcin concentrations.

**Patient Discontinuations, Adverse Events, and Concomitant Medication Evaluation:** No statistically significant difference in plasma raloxifene concentrations were identified for patients who discontinued treatment due to adverse events or death when compared to patients who continued treatment. The concentration range for these patients were all within the overall range observed for all patients who completed 36 months of treatment. No statistically significant relationship was identified between raloxifene concentration and leg cramps, vasodilatation, peripheral edema, or diabetes mellitus. The mean and range of plasma raloxifene concentrations in patients with these adverse events appear comparable to those for patients without these adverse events. The results of the current analyses confirmed the lack of effect of other highly glucuronidated drugs, highly protein-bound drugs, and other concomitant medications on plasma raloxifene concentrations.

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**Sponsor's Conclusions:**

**Pharmacokinetics:** Pharmacokinetic analyses of 0-36 month data of raloxifene treatment has revealed no new information affecting the raloxifene dose regimen. Raloxifene may be administered without regard to age, body weight, cigarette smoking, chronic alcohol use, and decreased renal function associated with aging as assessed by estimated creatinine clearance.

**Pharmacodynamics:** Raloxifene is an effective agent for treatment of osteoporosis in postmenopausal women and patients with the most significant disease had the greatest response to raloxifene. Results from the pharmacodynamic models of BMD favor 60 mg raloxifene HCl as the appropriate dose for the treatment of osteoporosis in postmenopausal women.

**Patient Discontinuations, Adverse Events, and Concomitant Medication Evaluations:** No significant effect of steady-state plasma raloxifene concentrations was identified on the occurrences of flu syndrome, vasodilatation, leg cramps, peripheral edema, uterine disorder, or diabetes mellitus. No significant effects of highly glucuronidated or highly protein-bound drugs on raloxifene plasma concentrations were identified. No significant or clinically relevant influence of concomitant medication on raloxifene plasma concentrations was identified in raloxifene-treated postmenopausal women taking various concomitant

medications. Other than cholestyramine, raloxifene may be administered without regard to concomitant medications.

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## APPENDIX 3 - PROTOCOL SUMMARY - Study H3S-MS-GGIP - Methylprednisolone Interaction

## ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

### Study No.: (H3S-MS-GGIP)

**Study Title:** A Cross-Over Study to Assess the Pharmacokinetic Interaction of Raloxifene after Multiple Administration, on Methylprednisolone Single Dose in Postmenopausal Women

**Investigator(s)/Center(s):** A single-center study conducted by Nils Brion, MD (Principal Investigator) and Myriam Marjoux-Fleure, MD (Co-Investigator) at VERSUS, 101-109 rue Jean Jaurès, 92300 Levallois Perret, France.

**Study Period**: The clinical phase corresponding to Study GGIP was October through December 1997.

**Objectives**: The primary objective of the study was to assess the effect of chronic administration of raloxifene on the plasma concentration profile of methylprednisolone given in a single oral dose. The secondary objective of the study was to assess the safety of coadministration of raloxifene and methylprednisolone.

**Study Design:** A randomized, balanced, placebo-controlled, two-treatment, two-period, crossover study. Treatment 1 consisted in multiple doses of raloxifene (Days 1 to 11) and a single dose of methylprednisolone on Day 11. For Treatment 2, raloxifene was replaced by placebo (Days 1 to 11) and similarly methylprednisolone was given on Day 11. Each subject received sequentially the two treatments in a randomized fashion, with an interval of 28 days between Day 1 of Period 1 and Day 1 of Period 2.

On Day 11 of each Period, sequential blood samples were obtained at the following times relative to dosing of methylprednisolone: 0 (predose), 1, 2, 4, 6, 9, 12, 16, 24, 28, and 32 hours in order to measure methylprednisolone for pharmacokinetic purposes. Two blood samples were obtained on Days 10 and 11 (predose of raloxifene) in order to document steady-state raloxifene plasma concentration.

**Subjects:** Sixteen healthy postmenopausal women, between the ages of 48 and 65 years, were enrolled and completed the study according to the protocol and data from all subjects were included in the pharmacokinetic and statistical analyses.

**Criteria for Inclusion:** Healthy postmenopausal women, of any ethnic origin, aged over 45 years

**Test Product, Dose and Mode of Administration, Batch and Formulation No.**: Raloxifene HCl was administered as 60-mg tablets, [redacted] Raloxifene HCl (or an equal number of placebo tablets) was given in doses of 120 mg (two tablets of 60 mg) twice daily from Day 1 to Day 4 and once daily from Days 5 to 11.

| Test Product[a] | Dose/Mode of Administration | Batch or Lot No. |
|---|---|---|
| Raloxifene HCl [a] | 2 x 60-mg tablets/oral [b] | B7533 |
| Placebo | tablets/oral [c] | 97390191 |

a Free base content was 92.85% of stated raloxifene HCl strength.
b The material was manufactured at Eli Lilly and Company Ltd, Kingsclere Road, Basingstoke, Hampshire, England.
c The material was provided by Lilly Clinical Operations, SA. Mont-Saint-Guibert, Belgium.

**Reference Therapy, Dose and Mode of Administration, Batch and Formulation No:**
Methylprednisolone was given to all subjects in doses of 32 mg (ie, two tablets of 16 mg) on Day 11 of Periods 1 and 2, and 30 minutes after the ingestion of the raloxifene or placebo tablets. Methylprednisolone marketed under the trade name Medrol Ê (Pharmacia - Upjohn) had been purchased by VERSUS and the same lot (26948, expiry date: 06/2000) was used throughout the study.

**Duration of Treatment**: Two treatment periods consistng of multiple doses of either raloxifene or placebo (Days 1 to 11) and a single dose of methylprednisolone on Day 11.

**Analytical Method(s) / Validation(s) / Analytical Center(s) / Dates of Analysis:**

| Analytical Method | Validation | Analytical Center | Dates Analyses |
|---|---|---|---|
| Raloxifene: [redacted] | Range: 0.050 to 5.030ng/mL; linear; CV and RE <10% | Lilly Laboratory for Bioanalytical Research, Toronto, Canada | 09 December 1997 |
| Methylprednisolone: [redacted] | Range: 4.00 to 800.00 ng/ml; linear; the precision (% CV) and the accuracy (expressed as the percentage difference) < 20 % | [redacted] | 15 January 1998 to 02 February 1998 |

**Plasma Sampling:**
Raloxifene - Days 10 and 11 of each Period - predose of raloxifene

Methylprednisolone - Day 11 of each period samples were collected at 0 (predose) and 1, 2, 4, 6, 9, 12, 16, 24, 28, and 32 hours postdose.

**Pharmacokinetic Methods**: For each plasma methylprednisolone concentration time-curve (Day 11 of each Period), the following parameters were derived: Cmax (observed peak concentration), tmax (time to Cmax), $t_{1/2}$ (half-life, defined as $t_{1/2} = \ln 2/\beta$), $AUC_{(0-\infty)}$ (area under the concentration time-curve, calculated by the trapezoidal rule), and Cl tot /F (apparent total clearance from plasma (after oral dosing)). Individual values of those parameters are reported as well as means, standard deviations and coefficients of variation. Predose plasma concentration data for raloxifene on Days 10 and 11 are reported.

**Statistical Methods**: The AUC (0-∞) and C max were used as primary variables to assess the pharmacokinetic interaction of repeated administration of raloxifene on methylprednisolone. The half life (t 1/2 ) and t max were also analyzed as secondary parameters. AUC (0-∞) and C max were log-transformed and submitted, together with t 1/2 , to an analysis of variance (ANOVA), suited to a two-way crossover design. The ANOVA model included fixed terms for sequence, period and treatment effects and subject as a random effect. Least square means for administrations with and without raloxifene and the 90% confidence interval for means differences between the two conditions were estimated from the ANOVA model. These 90% confidence limits were then compared to a pre-specified equivalence range defined as 70% to 143% for AUC (0-∞) and C max and as 70% to 130% for t 1/2 . This range was based on medical judgment taking into account between-subject variability in methylprednisolone pharmacokinetics. Variance components for the intersubject (between) and intrasubject (within) variability in these parameters was obtained through the mixed-effects linear model. The analysis of t max was based on a nonparametric method. Medians were reported for each treatment and t max was compared between treatments by a Wilcoxon signed rank test ignoring periods at the two-sided 5% level.

**Results**: The main pharmacokinetic metrics of methylprednisolone after a single oral dose of 32 mg were very similar in the two treatments:

**Pharmacokinetic Metrics of Methylprednisolone**

| | After Placebo [Mean ± SD] (n = 16) | After Raloxifene [Mean ± SD] (n = 16) |
|---|---|---|
| **Cmax (ng/mL)** | 277 ± 64 | 298 ± 91 |
| **tmax (h)** | 1.9 ± 1.0 | 1.6 ± 0.8 |
| **AUC (0-∞) (ng.h/mL)** | 1300 ± 540 | 1330 ± 590 |
| **Cl/F (L/h)** | 28 ± 9 | 29 ± 13 |
| **t 1/2 (h)** | 1.85 ± 0.43 | 1.85 ± 0.46 |

**Pharmacokinetic Interaction of Raloxifene on Methylprednisolone (M) after Repeated Administration of Raloxifene or Placebo**

| PK Metric for M | Between Subject CV (%) | Within Subject CV (%) | Mean Raloxifene Group (1) N = 16 | Mean Placebo Group (2 N = 16) | Ratio (1)/(2) | 90% Confidence Limits on Ratio | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| $AUC_{(0-\infty)}$ [a] ($ng/ml \times hr^{-1}$) | 42.5 | 13.6 | 1223 | 1214 | 100.8 | 92.7 | 109.7 |
| Cmax [a] (ng/ml) | 30.4 | 22.1 | 282.6 | 270.0 | 104.7 | 91.4 | 119.9 |
| t ½ [b] (hours) | 24.5 | 5.2 | 1.848 | 1.848 | 100.0 | 96.8 | 103.3 |
| | | Median Raloxifene group | | Median Placebo group | | | |
| tmax [c] (hours) | | 1.5 | | 2 | | (p-value = 0.5625) | |

a CV, geometric means, ratio and corresponding confidence limits are back-transformed from the logarithmic scale.
b for t 1/2, arithmetic means are reported.
c for tmax, medians and the two-sided p-value of the Wilcoxon signed rank test are reported.

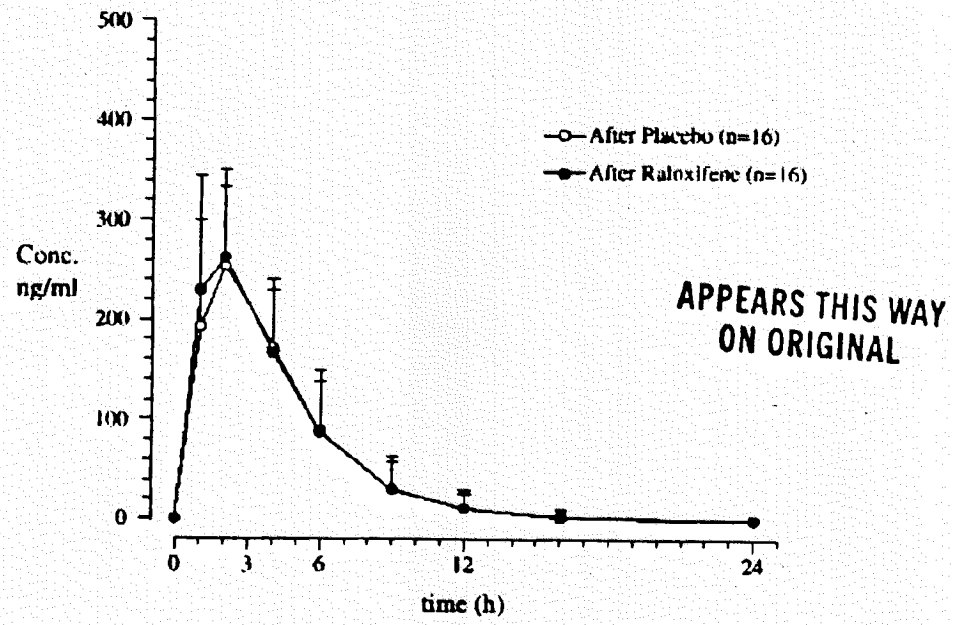


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**Figure GGIP.4.1. Mean (+ sd) Plasma Concentrations of Methylprednisolone Following a Single Oral Dose of 32 mg Methylprednisolone After Multiple Administration of Placebo or Raloxifene in 16 Postmenopausal Women**

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**Mean Raloxifene Predose Concentrations on Days 10 and 11 by Treatment Period**

| Concentration (ng/ml) Mean ± SD | |
|---|---|
| Treatment Period 1 N = 16 | Treatment Period 2 N = 16 |
| 0.93 ± 0.50 | 0.82 ± 0.47 |

Five subjects took 3 OTC medications in violation of the protocol. These were aspirin, acetaminophen and digedryl (a mixture of boldine and three inorganic salts. Visual inspection of the subjects who took either aspirin or digedryl showed now difference in plasma concentration profiles between treatments. Of the subjects who took acetaminophen there were no consistent changes in the plasma concentration profiles between treatments, i.e. increase, decrease or no change.

**Sponsor's Conclusions** The chronic administration of raloxifene, in postmenopausal women, has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose. No treatment-emergent adverse events were observed during the conduct of this study that would preclude further study of raloxifene HCl.

**Reviewer's Conclusions**

The only obvious drug related side effects were associated with methylprednisolone. No side effects clearly associated with raloxifene were apparent in the 16 subjects in this study.

Although it's not known if raloxifene -4,6- diglucuronide interferes with the methylprednisolone assay, it appears that the administration of raloxifene has no effect on the pharmacokinetics of methylprednisolone in postmenopausal women when given as a single oral dose. A demonstration by the sponsor of a lack of assay interference by raloxifene -4,6- diglucuronide is required before a conclusion of no effect of raloxifene on the pharmacokinetics of the parent compound methylprednisolone.

Conclusions regarding any effect on metabolite kinetics, specifically *methylprednisone*, or the lack thereof cannot be made. As the effect of raloxifene on *methylprednisone* is unknown and since *methylprednisone* is active, no conclusions can be made regarding whether there is an effect by raloxifene on the pharmacokinetics of methylprednisolone until the metabolite kinetics are examined.

Sampling for determination of raloxifene concentrations were limited and were only reported as a mean of two trough concentrations, one 24 hours before dosing with methylprednisolone and one immediately prior to dosing. Consequently, no determination of the effects of methylprednisolone on the pharmacokinetics of raloxifene can be made.

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## APPENDIX 4 - Analytic Validation - Raloxifene -

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## APPENDIX 5 - Analytic Validation - Raloxifene -

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# APPENDIX 6 - Analytic Validation - Methylprednisolone

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