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Topic: Technical report summarizing Mixed-Model Repeated Measures (MMRM) modeling strategies used to estimate and compare the rate of decline in eGFR as an end point for CKD clinical trials.

1. Introduction

This report is intended to summarize, based on the IDNT(CNTRL) study, results one might expect to see by adopting a Mixed-Model Repeated Measures (MMRM) approach using a change-from-baseline RM-ANOVA model or a change-from-baseline RM-ANCOVA model with an unstructured variance-covariance matrix. Per our conference call on October 27, 2023 we discussed reasons why the FDA is considering this as an alternative more nonparametric approach to the analysis of CKD clinical trial data compared to the more complex parametric two-slope mixed-effects modeling approach we have adopted. Having expressed my concerns about using a two-year study to assess drug treatment efficacy based on a MMRM approach, I took it upon myself to see what conclusions one would reach with this approach compared with the two-slope mixed-effects model as reported in our Statistics in Medicine (SIM) paper of 2019 as well as a two-slope marginal linear spline model with an unstructured variance-covariance matrix. Section 2 of this report provides a description of the data steps undertaken to perform a change-from-baseline MMRM ANOVA approach and a change-from-baseline MMRM ANCOVA approach followed by the results achieved with a marginal two-slope model with an unstructured covariance matrix. Section 3 of this report compares the results from these various models to that seen using our two-slope mixed-effects modeling approach as published in our 2019 SIM paper.

2. Data Structure for MMRM Models and a Marginal Linear Spline Model

This section describes the data steps taken to fit both a MMRM-ANOVA and a MMRM-ANCOVA to the IDNT(CNTRL) study along with a marginal two-slope linear spline model (each assuming an unstructured variance-covariance matrix) when follow-up is restricted to a two-year follow-up and a four-year follow-up. The original IDNT study design called for measurements at baseline (month=0), and months 3, 6, 12, 18, 24, 30, 36, 42 and 48 months. To fit a two-year and four-year MMRM-ANOVA model and MMRM-ANCOVA model, we need to define an appropriate window around actual patient visit times in order to center the times at 0, 3, 6, 12, 18, 24, 30, 36, 42 and 48 months. I ended up using a 50% width around the interval lengths between target times (i.e., 3 ± 1.5, 6 ± 1.5, 12 ± 3.0, 18 ± 3.0, 24 ± 3.0, …,48 ± 3.0) so as to minimize the number of missed visits. This resulted in losing only one observation per each of 17 subjects (4 controls and 13 treated) as shown in Appendix A.1. Appendix A.2 displays a partial listing of data for the control (Placebo) group and Appendix A.3 for the treated (ARB) group. Appendix A.4 lists those subjects whose target month (based on the 1.5 or 3 month window) exceeded the time-to-dropout but whose actual eGFR measurement was less than the time-to-dropout. Summary statistics (n, min, max, mean and standard deviation) are summarized in Table B.1 for the observed eGFR values and change from baseline eGFR values (i.e., eGFR(t) - eGFR(0)). Table B.2 summarizes the frequency and percentage of dropouts due to ESKD, Death, and ESKD or Death combined (the latter of which is less than the sum as we attribute dropout to the first event that occurs).

3. Marginal Models with an Unstructured Variance-Covariance Matrix

This section describes two models often used for MMRM analyses – a change from baseline RM-ANOVA model and the more efficient change from baseline RM-ANCOVA model. As described above, I created an IDNT dataset

using target visit times so as to fit both the MMRM-ANOVA and MMRM-ANCOVA models to the IDNT(CNTRL) study. This dataset was also used to fit a marginal two-slope linear spline model with the acute phase ending at month 3 (per our simplified two slope model used for our meta-analyses) and a second two-slope linear spline model with the acute phase ending at month 4 (per our Statistics in Medicine paper). Follow-up was restricted to a two-year period (24 months) and a four-year period (48 months). For both the MMRM-ANOVA model and the MMRM-ANCOVA model, I computed the least squares (LS) mean change from baseline value (in mL/min/1.73m^2) at each of the target visit times along with the corresponding LS mean change from baseline treatment effects (Treated – Control). In addition, I expressed the LS mean change from baseline treatment effects as treatment effects on the acute slope (corresponding to month 3) and as the treatment effects on total slopes (at selected post 3-month target visits times). The acute and total slope treatment effects were obtained by simply dividing the mean treatment effect by its corresponding target month. For example, the acute slope treatment effect per mL/min/1.73m^2/month was calculated as the mean treatment effect divided by 3 months while the total slope treatment effect at 24 months was calculated as the mean treatment effect divided by 24 months. The acute and total slope treatment effects were also expressed in units of mL/min/1.73m^2/year by simply multiplying the slope treatment effects on a per month basis by 12.

In addition to the MMRM-ANOVA and MMRM-ANCOVA models, I also fit a marginal linear spline model with an unstructured variance-covariance matrix using a change-point knot at month 3 (per our simplified two slope mixed-effects model used for the meta-analyses) and at month 4 (per our Statistics in Medicine paper).These analyses were done using the raw eGFR values based on a two-year study and a four-year study. Results are presented for the population-averaged intercepts, acute slopes, chronic slopes, change slopes and total slopes (at 24, 36 and 48 months). All analyses were carried out using likelihood-based methodology which provides valid inference assuming missing data are missing-at-random (MAR) but which can pose a major limitation when some or all of the missing data due to dropout are informative (i.e., missing not at random or MNAR).

Results

4.1. Two-Year Study Results for the MMRM Models:

Results of the MMRM ANOVA and ANCOVA analyses for a two-year study are presented in Tables 1a-1c for the ANOVA approach and Tables 2a-2c for the ANCOVA approach. Table 1a summarizes the LS ANOVA means while Table 1b summarizes the LS ANOVA mean treatment differences (i.e., effects) along with the corresponding acute and total slope effects. Table 1c summarizes the likelihood-based goodness-of-fit statistics. As shown in Table 1b, the only statistically significant treatment effect was that of an acute treatment effect seen at month 3 (both the mean difference and the acute slope effect) in favor of the control group (p=0.0437). There were no other significant treatment effects including the 24 month treatment effect and slope effect which the FDA would use to evaluate overall treatment efficacy. The MMRM-ANCOVA results in Tables 2a-2c mirror the results of the MMRM-ANOVA analysis in that the only significant treatment effect was that of the 3-montn acute treatment effect in favor of the control group (p=0.0363).

4.2. Four-Year Study Results for the MMRM Models:

Results of the MMRM ANOVA and ANCOVA analyses for a four-year study are presented in Tables 3a-3c for the ANOVA approach and Tables 4a-4c for the ANCOVA approach. Table 3a summarizes the LS ANOVA means while Table 3b summarizes the LS ANOVA mean treatment effects along with the corresponding acute and total slope effects. Table 3c summarizes the likelihood-based goodness-of-fit statistics. As shown in Table 3b, the only statistically significant treatment effects were that of an acute treatment effect seen at month 3 (both the mean difference and the acute slope effect) in favor of the control group (p=0.0429) and at month 48 (both the mean difference and the total slope effect) in favor of the treated group (p<0.0171). There were no other significant treatment effects including at any of the other time periods though a trend toward significance in favor of the treated group was seen at month 42 (p=0.0679). The MMRM-ANCOVA results in Tables 4a-4c mirror the results of the MMRM-ANOVA analysis in that there was a significant treatment effect seen at month 3 (both the mean difference and the acute slope effect) favoring the control group (p=0.0357) and at month 48 (both the mean difference and the total slope effect) favoring the treated group (p=0.0184) with a trend toward significance favoring the treated group at month 42 (p=0.0763).

4.3. Results for a Marginal Two-Slope Linear Spline Model:

Results of a two-year study when fitting a marginal two-slope linear spline model based on change point knots at 3 and 4 months are presented in Tables 5a-5b (for a knot at month 3) and Tables 5c-5d (for a knot at month 4). In all cases an unstructured covariance matrix was used to obtain robust estimates of variability and correlation. Table 5a presents the estimated intercept and slope parameters (acute slope, chronic slope, change slope and total slope assessed over a 24 month follow-up) for the control and treated groups along with their corresponding treatment effects (treated minus control) when the knot is fixed at 3 months. There were near significant differences in the chronic slopes (treated–control = 0.07128 mL/min/1.73m^2/month, p=0.0600) and change slopes (treated–control = 0.3904 mL/min/1.73m^2/month, p=0.0519) but less so for the difference in the acute slopes (treated–control = -0.3191 mL/min/1.73m^2/month, p=0.0900) and no evidence of a treatment effect on the two year total slope (treated–control = 0.02248 mL/min/1.73m^2/month, p=0.5291). Similar results shown in Table 5c were seen when the knot was fixed at 4 months. Despite having a lower AIC (see Tables 5b versus 5d) indicating a slightly better fit when the knot was fixed at 4 months, there were no significant treatment effects with respect to the acute slope (p=0.1832), chronic slope (p=0.0636), change slope (p=0.1027) or two-year total slope (p=0.4196).

Results of a four year study demonstrate the need for longer follow-up to achieve any sort of significant treatment effect as shown in Tables 6a-6b (for a knot at 3 months) and Tables 6c-6d (for a knot at 4 months) which is consistent with results from the MMRM-ANOVA and MMRM-ANCOVA models. In all cases an unstructured covariance matrix was used to obtain robust estimates of variability and correlation. Table 6a presents the estimated intercept and slope parameters (acute slope, chronic slope, change slope and total slopes assessed at 24, 36 and 48 months) for the control and treated groups along with their corresponding treatment effects (treated minus control) when the knot was fixed at 3 months. There was a near significant difference of -0.3411 mL/min/1.73m^2/month in the acute slope treatment effect in favor of the control group (p=0.0667) and significant differences in the chronic slope effect of 0.08096 mL/min/1.73m^2/month (p=0.0037) in favor of the treated group and in the change slope effect of 0.4221 mL/min/1.73m^2/month (p=0295). In terms of total slope treatment effects, while the two-year total slope treatment effect was not significant (0.02820 mL/min/1.73m^2/month, p=0.3452), nor the three-year total slope treatment effect (0.04580 mL/min/1.73m^2/month, p=0.0887), the four-year total slope treatment effect was significant (0.05458 mL/min/1.73m^2/month, p=0.0376).

Table 6c presents the estimated intercept and slope parameters (acute slope, chronic slope, change slope and total slope assessed at 24, 36 and 48 months) for the control and treated groups along with their corresponding treatment effects (treated minus control) when the knot was fixed at 4 months. As shown in Tables 6b versus 6d, a knot at 4 months provides a marginally better fit compared with a knot at 3 months. However, in terms of treatment effects, there was no significant treatment effect on the acute slope (a difference of -0.2216 mL/min/1.73m^2/month, p=0.1426), a marginal treatment effect on the change slope (a difference of 0.3040 mL/min/1.73m^2/month, p=0.0598) and a significant treatment effect on the chronic slope (a difference of 0.08240 mL/min/1.73m^2/month, p=0.0044). In terms of total slope treatment effects, neither the two-year total slope treatment effect (0.03172 mL/min/1.73m^2/month, p=0.2853) nor the three-year total slope treatment effect (0.04863 mL/min/1.73m^2/month, p=0.0671) were statistically significant whereas the four-year total slope treatment effect was significant (0.05708 mL/min/1.73m^2/month, p=0.0283).

4. Conclusions

Results of these analyses suggest that for the IDNT(CNTRL) study, which enrolled a relatively large number of 1,135 subjects (563 control patients and 572 treated patients), a two-year study would have been totally insufficient to demonstrate a positive treatment effect associated with the use of an angiotensin II receptor blocker (ARB) versus placebo control using either a MMRM-ANOVA or MMRM-ANCOVA approach and only borderline evidence of efficacy (p-values of 0.0600 and 0.0636) for a chronic slope treatment comparison for the two-slope model conducted over two years but no evidence of efficacy based on a total slope estimate. For a four-year study, estimates of a total slope effect (in mL/min/1.73m^2/month) for the ANOVA, ANCOVA and two-slope models all reached significance with the ANOVA and ANCOVA models yielding similar estimates of 0.08486±0.03553 (p=0.0171) and 0.08283±0.03058 (p=0.0184) compared with the two-slope model result of 0.05458±0.02622 (p=0.0376). Results for less the four years were not significant in all cases.

Table 1a
A MMRM analysis based on a Change From Baseline (CFB) ANOVA over 24 months
Least Squares (LS) Means expressed as eGFR Mean Change from Baseline (mL/min/1.73m^2)

Effect	*Trt*	*Month*	*Estimate*	*StdErr*	*DF*	*tValue*	*Probt*
Trt*Month	Control	3	-2.5630	0.4525	1070	-5.66	<.0001
Trt*Month	Control	6	-4.7966	0.4444	1070	-10.79	<.0001
Trt*Month	Control	12	-7.1936	0.5158	1070	-13.95	<.0001
Trt*Month	Control	18	-10.1052	0.5937	1070	-17.02	<.0001
Trt*Month	Control	24	-12.4595	0.6304	1070	-19.76	<.0001
Trt*Month	Treated	3	-3.8501	0.4491	1070	-8.57	<.0001
Trt*Month	Treated	6	-5.2331	0.4424	1070	-11.83	<.0001
Trt*Month	Treated	12	-7.8670	0.5117	1070	-15.37	<.0001
Trt*Month	Treated	18	-10.2616	0.5893	1070	-17.41	<.0001
Trt*Month	Treated	24	-11.9059	0.6242	1070	-19.07	<.0001

Table 1b
A MMRM analysis based on a Change From Baseline (CFB) ANOVA over 24 months
Mean Treatment Effect = Treated-Control Mean CFB (mL/min/1.73m^2)
Acute and Total Slope Effects = Mean Treatment Effect/Time (mL/min/1.73m^2/Time)
where Time is in units of either Month or Year

StmtNo	*Effect*	*Label*	*Estimate*	*StdErr*	*DF*	*tValue*	*Probt*
1	Trt*Month	Mean Trt Effect at Month= 3	-1.2871	0.6375	1070	-2.02	0.0437
2	Trt*Month	Mean Trt Effect at Month= 6	-0.4365	0.6271	1070	-0.70	0.4865
3	Trt*Month	Mean Trt Effect at Month=12	-0.6734	0.7266	1070	-0.93	0.3542
4	Trt*Month	Mean Trt Effect at Month=18	-0.1565	0.8365	1070	-0.19	0.8517
5	Trt*Month	Mean Trt Effect at Month=24	0.5535	0.8871	1070	0.62	0.5328
6	Trt*Month	Acute Slope Effect/Month at Month 3	-0.4290	0.2125	1070	-2.02	0.0437
7	Trt*Month	Total Slope Effect/Month at Month 12	-0.05611	0.06055	1070	-0.93	0.3542
8	Trt*Month	Total Slope Effect/Month at Month 24	0.02306	0.03696	1070	0.62	0.5328
9	Trt*Month	Acute Slope Effect/Year at Month 3	-5.1483	2.5501	1070	-2.02	0.0437
10	Trt*Month	Total Slope Effect/Year at Month 12	-0.6734	0.7266	1070	-0.93	0.3542
11	Trt*Month	Total Slope Effect/Year at Month 24	0.2768	0.4436	1070	0.62	0.5328

Table 1c
A MMRM analysis based on a Change From Baseline (CFB) ANOVA over 24 months
Goodness-of_Fit Criteria

Neg2LogLike	*Parms*	*AIC*	*AICC*	*HQIC*	*BIC*	*CAIC*
30520.7	15	30550.7	30550.8	30579.0	30625.3	30640.3

Table 2a
A MMRM analysis based on a Change From Baseline (CFB) ANCOVA over 24 months
Least Squares (LS) Means expressed as eGFR Mean Change from Baseline (mL/min/1.73m^2)

Effect	*Trt*	*Month*	*Estimate*	*StdErr*	*DF*	*tValue*	*Probt*
Trt*Month	Control	3	-2.6515	0.4436	1069	-5.98	<.0001
Trt*Month	Control	6	-4.8612	0.4380	1069	-11.10	<.0001
Trt*Month	Control	12	-7.2372	0.5055	1069	-14.32	<.0001
Trt*Month	Control	18	-10.1266	0.5781	1069	-17.52	<.0001
Trt*Month	Control	24	-12.4224	0.6136	1069	-20.25	<.0001
Trt*Month	Treated	3	-3.9609	0.4403	1069	-9.00	<.0001
Trt*Month	Treated	6	-5.3215	0.4361	1069	-12.20	<.0001
Trt*Month	Treated	12	-7.9506	0.5015	1069	-15.85	<.0001
Trt*Month	Treated	18	-10.3384	0.5737	1069	-18.02	<.0001
Trt*Month	Treated	24	-11.9470	0.6074	1069	-19.67	<.0001

Table 2b
A MMRM analysis based on a Change From Baseline (CFB) ANCOVA over 24 months
Mean Treatment Effect = Treated-Control Mean CFB in mL/min/1.73m^2
Acute and Total Slope Effects = Mean Treatment Effect/Time in mL/min/1.73m^2/Time
where Time is in units of either Months or Years

StmtNo	*Effect*	*Label*	*Estimate*	*StdErr*	*DF*	*tValue*	*Probt*
1	Trt*Month	Mean Trt Effect at Month= 3	-1.3094	0.6247	1069	-2.10	0.0363
2	Trt*Month	Mean Trt Effect at Month= 6	-0.4603	0.6179	1069	-0.74	0.4565
3	Trt*Month	Mean Trt Effect at Month=12	-0.7133	0.7120	1069	-1.00	0.3166
4	Trt*Month	Mean Trt Effect at Month=18	-0.2118	0.8144	1069	-0.26	0.7949
5	Trt*Month	Mean Trt Effect at Month=24	0.4754	0.8633	1069	0.55	0.5820
6	Trt*Month	Acute Slope Effect/Month at Month 3	-0.4365	0.2082	1069	-2.10	0.0363
7	Trt*Month	Total Slope Effect/Month at Month 12	-0.05944	0.05933	1069	-1.00	0.3166
8	Trt*Month	Total Slope Effect/Month at Month 24	0.01981	0.03597	1069	0.55	0.5820
9	Trt*Month	Acute Slope Effect/Year at Month 3	-5.2374	2.4990	1069	-2.10	0.0363
10	Trt*Month	Total Slope Effect/Year at Month 12	-0.7133	0.7120	1069	-1.00	0.3166
11	Trt*Month	Total Slope Effect/Year at Month 24	0.2377	0.4317	1069	0.55	0.5820

Table 2c
A MMRM analysis based on a Change From Baseline (CFB) ANCOVA over 24 months
Goodness-of_Fit Criteria

Neg2LogLike	*Parms*	*AIC*	*AICC*	*HQIC*	*BIC*	*CAIC*
30470.2	15	30500.2	30500.3	30528.4	30574.8	30589.8

Table 3a
A MMRM analysis based on a Change from Baseline (CFB) ANOVA over 48 months
Least Squares (LS) Means expressed as eGFR Mean Change from Baseline (mL/min/1.73m^2)

Effect	*Trt*	*Month*	*Estimate*	*StdErr*	*DF*	*tValue*	*Probt*
Trt*Month	Control	3	-2.5697	0.4521	1071	-5.68	<.0001
Trt*Month	Control	6	-4.7899	0.4442	1071	-10.78	<.0001
Trt*Month	Control	12	-7.1619	0.5150	1071	-13.91	<.0001
Trt*Month	Control	18	-10.0982	0.5924	1071	-17.05	<.0001
Trt*Month	Control	24	-12.4153	0.6268	1071	-19.81	<.0001
Trt*Month	Control	30	-14.0138	0.6811	1071	-20.58	<.0001
Trt*Month	Control	36	-15.5861	0.8391	1071	-18.57	<.0001
Trt*Month	Control	42	-18.3899	1.0459	1071	-17.58	<.0001
Trt*Month	Control	48	-21.7911	1.2613	1071	-17.28	<.0001
Trt*Month	Treated	3	-3.8608	0.4488	1071	-8.60	<.0001
Trt*Month	Treated	6	-5.2246	0.4422	1071	-11.81	<.0001
Trt*Month	Treated	12	-7.8687	0.5111	1071	-15.39	<.0001
Trt*Month	Treated	18	-10.2820	0.5877	1071	-17.49	<.0001
Trt*Month	Treated	24	-11.9997	0.6192	1071	-19.38	<.0001
Trt*Month	Treated	30	-13.1391	0.6686	1071	-19.65	<.0001
Trt*Month	Treated	36	-14.9870	0.8079	1071	-18.55	<.0001
Trt*Month	Treated	42	-15.7811	0.9716	1071	-16.24	<.0001
Trt*Month	Treated	48	-17.7177	1.1478	1071	-15.44	<.0001

Table 3b
A MMRM analysis based on a Change from Baseline (CFB) ANOVA over 48 months
Mean Treatment Effect = Treated-Control Mean CFB in mL/min/1.73m^2
Acute and Total Slope Effects = Mean Treatment Effect/Time in mL/min/1.73m^2/Time
where Time is in units of either Months or Years

StmtNo	Effect	Label	Estimate	StdErr	DF	tValue	Probt
1	Trt*Month	Mean Trt Effect at Month= 3	-1.2911	0.6370	1071	-2.03	0.0429
2	Trt*Month	Mean Trt Effect at Month= 6	-0.4348	0.6268	1071	-0.69	0.4881
3	Trt*Month	Mean Trt Effect at Month=12	-0.7067	0.7256	1071	-0.97	0.3303
4	Trt*Month	Mean Trt Effect at Month=18	-0.1838	0.8345	1071	-0.22	0.8257
5	Trt*Month	Mean Trt Effect at Month=24	0.4156	0.8810	1071	0.47	0.6372
6	Trt*Month	Mean Trt Effect at Month=30	0.8746	0.9544	1071	0.92	0.3597
7	Trt*Month	Mean Trt Effect at Month=36	0.5991	1.1648	1071	0.51	0.6071
8	Trt*Month	Mean Trt Effect at Month=42	2.6088	1.4275	1071	1.83	0.0679
9	Trt*Month	Mean Trt Effect at Month=48	4.0734	1.7054	1071	2.39	0.0171
10	Trt*Month	Acute Slope Effect/Month at Month 3	-0.4304	0.2123	1071	-2.03	0.0429
11	Trt*Month	Total Slope Effect/Month at Month 12	-0.05889	0.06046	1071	-0.97	0.3303
12	Trt*Month	Total Slope Effect/Month at Month 24	0.01732	0.03671	1071	0.47	0.6372
13	Trt*Month	Total Slope Effect/Month at Month 36	0.01664	0.03235	1071	0.51	0.6071
14	Trt*Month	Total Slope Effect/Month at Month 48	0.08486	0.03553	1071	2.39	0.0171
15	Trt*Month	Acute Slope Effect/Year at Month 3	-5.1644	2.5480	1071	-2.03	0.0429
16	Trt*Month	Total Slope Effect/Year at Month 12	-0.7067	0.7256	1071	-0.97	0.3303
17	Trt*Month	Total Slope Effect/Year at Month 24	0.2078	0.4405	1071	0.47	0.6372
18	Trt*Month	Total Slope Effect/Year at Month 36	0.1997	0.3883	1071	0.51	0.6071
19	Trt*Month	Total Slope Effect/Year at Month 48	1.0184	0.4263	1071	2.39	0.0171

Table 3c
A MMRM analysis based on a Change from Baseline (CFB) ANOVA over 48 months
Goodness-of_Fit Criteria

Neg2LogLike	Parms	AIC	AICC	HQIC	BIC	CAIC
38597.0	45	38687.0	38687.8	38771.9	38911.1	38956.1

Table 4a
A MMRM analysis based on a Change from Baseline (CFB) ANCOVA over 48 months
Least Squares (LS) Means expressed as eGFR Mean Change from Baseline (mL/min/1.73m^2)

Effect	*Trt*	*Month*	*Estimate*	*StdErr*	*DF*	*tValue*	*Probt*
Trt*Month	Control	3	-2.7279	0.4435	1070	-6.15	<.0001
Trt*Month	Control	6	-4.9246	0.4379	1070	-11.24	<.0001
Trt*Month	Control	12	-7.2780	0.5050	1070	-14.41	<.0001
Trt*Month	Control	18	-10.1927	0.5771	1070	-17.66	<.0001
Trt*Month	Control	24	-12.4568	0.6103	1070	-20.41	<.0001
Trt*Month	Control	30	-14.0312	0.6696	1070	-20.95	<.0001
Trt*Month	Control	36	-15.5669	0.8251	1070	-18.87	<.0001
Trt*Month	Control	42	-18.3950	1.0349	1070	-17.77	<.0001
Trt*Month	Control	48	-21.6609	1.2463	1070	-17.38	<.0001
Trt*Month	Treated	3	-4.0407	0.4403	1070	-9.18	<.0001
Trt*Month	Treated	6	-5.3821	0.4361	1070	-12.34	<.0001
Trt*Month	Treated	12	-8.0198	0.5013	1070	-16.00	<.0001
Trt*Month	Treated	18	-10.4259	0.5726	1070	-18.21	<.0001
Trt*Month	Treated	24	-12.1142	0.6029	1070	-20.09	<.0001
Trt*Month	Treated	30	-13.2305	0.6572	1070	-20.13	<.0001
Trt*Month	Treated	36	-15.0637	0.7936	1070	-18.98	<.0001
Trt*Month	Treated	42	-15.8911	0.9600	1070	-16.55	<.0001
Trt*Month	Treated	48	-17.6849	1.1320	1070	-15.62	<.0001

Table 4b
A MMRM analysis based on a Change from Baseline (CFB) ANCOVA over 48 months
Mean Treatment Effect = Treated-Control Mean CFB in mL/min/1.73m^2
Acute and Total Slope Effects = Mean Treatment Effect/Time in mL/min/1.73m^2/Time
where Time is in units of either Months or Years

StmtNo	Effect	Label	Estimate	StdErr	DF	tValue	Probt
1	Trt*Month	Mean Trt Effect at Month= 3	-1.3127	0.6242	1070	-2.10	0.0357
2	Trt*Month	Mean Trt Effect at Month= 6	-0.4575	0.6175	1070	-0.74	0.4589
3	Trt*Month	Mean Trt Effect at Month=12	-0.7418	0.7111	1070	-1.04	0.2971
4	Trt*Month	Mean Trt Effect at Month=18	-0.2332	0.8125	1070	-0.29	0.7741
5	Trt*Month	Mean Trt Effect at Month=24	0.3426	0.8576	1070	0.40	0.6896
6	Trt*Month	Mean Trt Effect at Month=30	0.8007	0.9381	1070	0.85	0.3935
7	Trt*Month	Mean Trt Effect at Month=36	0.5032	1.1447	1070	0.44	0.6603
8	Trt*Month	Mean Trt Effect at Month=42	2.5039	1.4114	1070	1.77	0.0763
9	Trt*Month	Mean Trt Effect at Month=48	3.9760	1.6836	1070	2.36	0.0184
10	Trt*Month	Acute Slope Effect/Month at Month 3	-0.4376	0.2081	1070	-2.10	0.0357
11	Trt*Month	Total Slope Effect/Month at Month 12	-0.06182	0.05926	1070	-1.04	0.2971
12	Trt*Month	Total Slope Effect/Month at Month 24	0.01428	0.03573	1070	0.40	0.6896
13	Trt*Month	Total Slope Effect/Month at Month 36	0.01398	0.03180	1070	0.44	0.6603
14	Trt*Month	Total Slope Effect/Month at Month 48	0.08283	0.03508	1070	2.36	0.0184
15	Trt*Month	Acute Slope Effect/Year at Month 3	-5.2509	2.4968	1070	-2.10	0.0357
16	Trt*Month	Total Slope Effect/Year at Month 12	-0.7418	0.7111	1070	-1.04	0.2971
17	Trt*Month	Total Slope Effect/Year at Month 24	0.1713	0.4288	1070	0.40	0.6896
18	Trt*Month	Total Slope Effect/Year at Month 36	0.1677	0.3816	1070	0.44	0.6603
19	Trt*Month	Total Slope Effect/Year at Month 48	0.9940	0.4209	1070	2.36	0.0184

Table 4c
A MMRM analysis based on a Change from Baseline (CFB) ANCOVA over 48 months
Goodness-of_Fit Criteria

Neg2LogLike	Parms	AIC	AICC	HQIC	BIC	CAIC
38547.5	45	38637.5	38638.2	38722.3	38861.5	38906.5

Table 5a: Estimated Slopes (ml/min/1.73m^2/month) and Treatment Effects for a Marginal Linear Spline Model (Knot=3 months) with an Unstructured Covariance Matrix. Results are based on a 2 year (24 month) IDNT Follow-Up Period

Treatment Slope Effects (per Month)	*Estimate*	*Standard Error*	*DF*	*t Value*	*p-value*
Intercept Control (C)	50.6082	0.8197	1133	61.74	<.0001
Intercept Treated (T)	49.8098	0.8132	1133	61.25	<.0001
Intercept Diff.(T-C)	-0.7983	1.1546	1133	-0.69	0.4894
Acute Slope Control (C), < 3 months	-0.9994	0.1335	1133	-7.49	<.0001
Acute Slope Treated (T), < 3 months	-1.3185	0.1325	1133	-9.95	<.0001
Acute Slope Diff. (T-C), < 3 months	-0.3191	0.1881	1133	-1.70	0.0900
Chronic Slope Control(C),> 3 months	-0.4516	0.02693	1133	-16.77	<.0001
Chronic Slope Treated(T),> 3 months	-0.3803	0.02661	1133	-14.29	<.0001
Chronic Slope Diff.(T-C),> 3 months	0.07128	0.03786	1133	1.88	0.0600
Change Slope Control(C)	0.5478	0.1424	1133	3.85	0.0001
Change Slope Treated(T)	0.9382	0.1412	1133	6.64	<.0001
Change Slope Diff.(T-C)	0.3904	0.2006	1133	1.95	0.0519
Total Slope Control(C) at 24 months	-0.5201	0.02535	1133	-20.52	<.0001
Total Slope Treated(T) at 24 months	-0.4976	0.02515	1133	-19.79	<.0001
Total Slope Diff.(T-C) at 24 months	0.02248	0.03570	1133	0.63	0.5291

Table 5b: Goodness-of-Fit Criteria
Marginal Linear Spline Model (Knot=3 months) with an Unstructured Covariance Matrix. Results based on a 2 year (24 month) IDNT Follow-Up Period

Neg2LogLike	*Parms*	*AIC*	*AICC*	*HQIC*	*BIC*	*CAIC*
40426.1	21	40468.1	40468.3	40508.0	40573.8	40594.8

Table 5c: Estimated Slopes (ml/min/1.73m^2/month) and Treatment Effects for a Marginal Linear Spline Model (Knot=4 months) with an Unstructured Covariance Matrix. Results are based on a 2 year (24 month) IDNT Follow-Up Period

Treatment Slope Effects (per Month)	*Estimate*	*Standard Error*	*DF*	*t Value*	*p-value*
Intercept Control (C)	50.5936	0.8172	1133	61.91	<.0001
Intercept Treated (T)	49.7002	0.8107	1133	61.31	<.0001
Intercept Diff.(T-C)	-0.8934	1.1511	1133	-0.78	0.4378
Acute Slope Control (C), < 4 months	-0.9522	0.1097	1133	-8.68	<.0001
Acute Slope Treated (T), < 4 months	-1.1581	0.1089	1133	-10.63	<.0001
Acute Slope Diff. (T-C), < 4 months	-0.2058	0.1546	1133	-1.33	0.1832
Chronic Slope Control(C),> 4 months	-0.4291	0.02885	1133	-14.87	<.0001
Chronic Slope Treated(T),> 4 months	-0.3538	0.02848	1133	-12.42	<.0001
Chronic Slope Diff.(T-C),> 4 months	0.07527	0.04054	1133	1.86	0.0636
Change Slope Control(C)	0.5232	0.1222	1133	4.28	<.0001
Change Slope Treated(T)	0.8043	0.1212	1133	6.64	<.0001
Change Slope Diff.(T-C)	0.2811	0.1721	1133	1.63	0.1027
Total Slope Control(C) at 24 months	-0.5163	0.02498	1133	-20.67	<.0001
Total Slope Treated(T) at 24 months	-0.4879	0.02478	1133	-19.69	<.0001
Total Slope Diff.(T-C) at 24 months	0.02841	0.03518	1133	0.81	0.4196

Table 5d: Goodness-of-Fit Criteria
Marginal Linear Spline Model (Knot=4 months) with an Unstructured Covariance Matrix. Results based on a 2 year (24 month) IDNT Follow-Up Period

Neg2LogLike	*Parms*	*AIC*	*AICC*	*HQIC*	*BIC*	*CAIC*
40423.2	21	40465.2	40465.4	40505.2	40570.9	40591.9

Table 6a: Estimated Slopes (ml/min/1.73m^2/month) and Treatment Effects for a Marginal Linear Spline Model (Knot=3 months) with an Unstructured Covariance Matrix. Results are based on a 4 year (48 month) IDNT Follow-Up Period

Treatment Slope Effects (per Month)	*Estimate*	*Standard Error*	*DF*	*t Value*	*p-value*
Intercept Control (C)	50.3690	0.8149	1133	61.81	<.0001
Intercept Treated (T)	49.6334	0.8081	1133	61.42	<.0001
Intercept Diff.(T-C)	-0.7355	1.1476	1133	-0.64	0.5217
Acute Slope Control (C), < 3 months	-1.0432	0.1319	1133	-7.91	<.0001
Acute Slope Treated (T), < 3 months	-1.3844	0.1309	1133	-10.58	<.0001
Acute Slope Diff. (T-C), < 3 months	-0.3411	0.1858	1133	-1.84	0.0667
Chronic Slope Control(C),> 3 months	-0.4017	0.02005	1133	-20.03	<.0001
Chronic Slope Treated(T),> 3 months	-0.3207	0.01934	1133	-16.59	<.0001
Chronic Slope Diff.(T-C),> 3 months	0.08096	0.02786	1133	2.91	0.0037
Change Slope Control(C)	0.6415	0.1377	1133	4.66	<.0001
Change Slope Treated(T)	1.0636	0.1362	1133	7.81	<.0001
Change Slope Diff.(T-C)	0.4221	0.1937	1133	2.18	0.0295
Total Slope Control(C) at 24 months	-0.4819	0.02130	1133	-22.63	<.0001
Total Slope Treated(T) at 24 months	-0.4537	0.02093	1133	-21.67	<.0001
Total Slope Diff.(T-C) at 24 months	0.02820	0.02986	1133	0.94	0.3452
Total Slope Control(C) at 36 months	-0.4551	0.01925	1133	-23.65	<.0001
Total Slope Treated(T) at 36 months	-0.4093	0.01877	1133	-21.81	<.0001
Total Slope Diff.(T-C) at 36 months	0.04580	0.02688	1133	1.70	0.0887
Total Slope Control(C) at 48 months	-0.4418	0.01881	1133	-23.49	<.0001
Total Slope Treated(T) at 48 months	-0.3872	0.01826	1133	-21.20	<.0001
Total Slope Diff.(T-C) at 48 months	0.05458	0.02622	1133	2.08	0.0376

Table 6b: Goodness-of-Fit Criteria
Marginal Linear Spline Model (Knot=3 months) with an Unstructured Covariance Matrix. Results are based on a 4 year (48 month) IDNT Follow-Up Period

Neg2LogLike	*Parms*	*AIC*	*AICC*	*HQIC*	*BIC*	*CAIC*
48530.7	55	48640.7	48641.6	48745.3	48917.6	48972.6

Table 6c: Estimated Slopes (ml/min/1.73m^2/month) and Treatment Effects for a Marginal Linear Spline Model (Knot=4 months) with an Unstructured Covariance Matrix. Results are based on a 4 year (48 month) IDNT Follow-Up Period

Treatment Slope Effects (per Month)	*Estimate*	*Standard Error*	*DF*	*t Value*	*p-value*
Intercept Control (C)	50.4208	0.8132	1133	62.00	<.0001
Intercept Treated (T)	49.6022	0.8065	1133	61.50	<.0001
Intercept Diff.(T-C)	-0.8186	1.1453	1133	-0.71	0.4749
Acute Slope Control (C), < 4 months	-0.9988	0.1072	1133	-9.32	<.0001
Acute Slope Treated (T), < 4 months	-1.2204	0.1064	1133	-11.47	<.0001
Acute Slope Diff. (T-C), < 4 months	-0.2216	0.1510	1133	-1.47	0.1426
Chronic Slope Control(C),> 4 months	-0.3845	0.02079	1133	-18.49	<.0001
Chronic Slope Treated(T),> 4 months	-0.3021	0.02001	1133	-15.09	<.0001
Chronic Slope Diff.(T-C),> 4 months	0.08240	0.02886	1133	2.86	0.0044
Change Slope Control(C)	0.6143	0.1148	1133	5.35	<.0001
Change Slope Treated(T)	0.9183	0.1134	1133	8.10	<.0001
Change Slope Diff.(T-C)	0.3040	0.1613	1133	1.88	0.0598
Total Slope Control(C) at 24 months	-0.4869	0.02115	1133	-23.02	<.0001
Total Slope Treated(T) at 24 months	-0.4551	0.02082	1133	-21.86	<.0001
Total Slope Diff.(T-C) at 24 months	0.03172	0.02968	1133	1.07	0.2853
Total Slope Control(C) at 36 months	-0.4527	0.01900	1133	-23.83	<.0001
Total Slope Treated(T) at 36 months	-0.4041	0.01852	1133	-21.82	<.0001
Total Slope Diff.(T-C) at 36 months	0.04863	0.02653	1133	1.83	0.0671
Total Slope Control(C) at 48 months	-0.4356	0.01866	1133	-23.34	<.0001
Total Slope Treated(T) at 48 months	-0.3785	0.01810	1133	-20.91	<.0001
Total Slope Diff.(T-C) at 48 months	0.05708	0.02600	1133	2.20	0.0283

Table 6d: Goodness-of-Fit Criteria
Marginal Linear Spline Model (Knot=4 months) with an Unstructured Covariance Matrix. Results are based on a 4 year (48 month) IDNT Follow-Up Period

Neg2LogLike	*Parms*	*AIC*	*AICC*	*HQIC*	*BIC*	*CAIC*
48520.3	55	48630.3	48631.3	48734.9	48907.2	48962.2

Appendix A.1: List of subjects with missing observations for the 6 month visit or with and extraneous eGFR measurement

Study ID	*Study Name*	*Treatment Group*	*Subject*	*Recorded Month*	*Timing Window*	*Month*	*Baseline eGFR (eGFR0)*	*eGFR*	*Cause of Dropout*
29	IDNT(CNTRL)	Control	189	0.03333	1.5	.	38.3069	43.5050	Censored
29	IDNT(CNTRL)	Control	401	7.96667	1.5	.	30.6128	24.8981	Censored
29	IDNT(CNTRL)	Control	657	0.03333	1.5	.	44.1238	40.8524	Censored
29	IDNT(CNTRL)	Control	659	8.13333	1.5	.	60.7298	66.7256	Censored
29	IDNT(CNTRL)	Treated	94	8.96667	1.5	.	64.7430	59.8526	Censored
29	IDNT(CNTRL)	Treated	134	0.06667	1.5	.	36.7236	26.8576	ESKD
29	IDNT(CNTRL)	Treated	143	0.06667	1.5	.	68.3202	68.4631	Censored
29	IDNT(CNTRL)	Treated	178	0.13333	1.5	.	33.3696	33.6344	Censored
29	IDNT(CNTRL)	Treated	209	0.06667	1.5	.	19.9053	23.0797	Censored
29	IDNT(CNTRL)	Treated	276	7.96667	1.5	.	74.3336	83.2539	Censored
29	IDNT(CNTRL)	Treated	374	7.96667	1.5	.	71.3672	52.7270	Censored
29	IDNT(CNTRL)	Treated	403	0.13333	1.5	.	57.5030	63.0674	Censored
29	IDNT(CNTRL)	Treated	614	7.90000	1.5	.	31.4425	12.4754	ESKD
29	IDNT(CNTRL)	Treated	660	8.13333	1.5	.	51.8018	47.9122	Censored
29	IDNT(CNTRL)	Treated	802	7.53333	1.5	.	75.3547	75.1840	Censored
29	IDNT(CNTRL)	Treated	939	7.66667	1.5	.	47.0920	24.8286	Censored
29	IDNT(CNTRL)	Treated	1126	0.06667	1.5	.	58.3137	63.9591	Censored

Appendix A.2: Partial listing of IDNT data for control subjects with cause of dropout. Mean baseline eGFR0=51.5673 mL/min/1.73m^2 (Control=51.8253, Treated=51.3205)

Subject	*Treatment Group*	*Recorded Month*	*Timing Window*	*Month*	*eGFR*	*CFB eGFR*	*Cause of Dropout*
1	Control	0.0000	1.5	0	71.7513	0.0000	Censored
1	Control	2.8333	1.5	3	65.2111	-6.5402	Censored
1	Control	5.9000	1.5	6	54.8235	-16.9278	Censored
1	Control	11.9333	3.0	12	71.4053	-0.3460	Censored
1	Control	18.5000	3.0	18	64.6178	-7.1335	Censored
1	Control	24.6667	3.0	24	46.6642	-25.0871	Censored
1	Control	30.5333	3.0	30	50.0140	-21.7373	Censored
1	Control	36.1667	3.0	36	46.3522	-25.3991	Censored
1	Control	42.0667	3.0	42	43.1308	-28.6205	Censored
1	Control	48.3333	3.0	48	33.7769	-37.9744	Censored
4	Control	0.0000	1.5	0	42.6959	0.0000	Death
4	Control	3.2333	1.5	3	54.0801	11.3842	Death
6	Control	0.0000	1.5	0	70.2602	0.0000	ESKD
6	Control	3.2667	1.5	3	63.8398	-6.4204	ESKD
6	Control	6.0667	1.5	6	58.3123	-11.9479	ESKD
6	Control	12.5333	3.0	12	69.8970	-0.3633	ESKD
6	Control	18.2000	3.0	18	63.2861	-6.9741	ESKD
6	Control	24.0000	3.0	24	63.0723	-7.1879	ESKD
6	Control	36.4000	3.0	36	39.7123	-30.5479	ESKD
6	Control	42.4333	3.0	42	35.0944	-35.1658	ESKD
8	Control	0.0000	1.5	0	54.7293	0.0000	Censored
10	Control	0.0000	1.5	0	59.9449	0.0000	Censored
10	Control	6.2000	1.5	6	42.4669	-17.4779	Censored
11	Control	0.0000	1.5	0	29.9698	0.0000	ESKD
11	Control	4.2667	1.5	3	45.5986	15.6288	ESKD
11	Control	6.6000	1.5	6	35.3375	5.3677	ESKD
11	Control	12.2000	3.0	12	35.2222	5.2524	ESKD
11	Control	19.2000	3.0	18	37.1938	7.2240	ESKD
11	Control	24.8000	3.0	24	28.3635	-1.6063	ESKD
11	Control	30.6333	3.0	30	21.0199	-8.9499	ESKD

Appendix A.3: Partial listing of IDNT data for treated subjects with cause of dropout. Mean baseline eGFR0=51.5673 mL/min/1.73m^2 (Control=51.8253, Treated=51.3205)

Subject	*Treatment Group*	*Recorded Month*	*Timing Window*	*Month*	*eGFR*	*Baseline eGFR (eGFR0)*	*CFB eGFR*	*Cause of Dropout*
2	Treated	0.0000	1.5	0	95.2622	95.2622	0.0000	Censored
2	Treated	3.5000	1.5	3	95.1141	95.2622	-0.1480	Censored
2	Treated	6.5333	1.5	6	84.6848	95.2622	-10.5774	Censored
2	Treated	11.6667	3.0	12	84.4316	95.2622	-10.8306	Censored
2	Treated	18.2000	3.0	18	68.8318	95.2622	-26.4304	Censored
2	Treated	23.8000	3.0	24	68.6073	95.2622	-26.6549	Censored
2	Treated	30.0000	3.0	30	83.5334	95.2622	-11.7287	Censored
2	Treated	36.8000	3.0	36	68.0890	95.2622	-27.1732	Censored
2	Treated	42.6667	3.0	42	52.8906	95.2622	-42.3715	Censored
2	Treated	48.3000	3.0	48	56.9621	95.2622	-38.3001	Censored
3	Treated	0.0000	1.5	0	35.4170	35.4170	0.0000	Censored
3	Treated	3.1000	1.5	3	44.3687	35.4170	8.9517	Censored
3	Treated	5.9000	1.5	6	41.7773	35.4170	6.3603	Censored
3	Treated	12.6667	3.0	12	37.3092	35.4170	1.8922	Censored
3	Treated	30.4000	3.0	30	31.8734	35.4170	-3.5436	Censored
3	Treated	36.4667	3.0	36	30.3545	35.4170	-5.0625	Censored
5	Treated	0.0000	1.5	0	46.9179	46.9179	0.0000	Censored
5	Treated	5.6333	1.5	6	40.7921	46.9179	-6.1257	Censored
5	Treated	19.7000	3.0	18	43.3312	46.9179	-3.5866	Censored
7	Treated	0.0000	1.5	0	67.3704	67.3704	0.0000	Censored
7	Treated	2.9000	1.5	3	51.5664	67.3704	-15.8041	Censored
7	Treated	5.9333	1.5	6	47.6391	67.3704	-19.7313	Censored
7	Treated	12.2333	3.0	12	47.4643	67.3704	-19.9061	Censored
7	Treated	18.0667	3.0	18	47.3031	67.3704	-20.0673	Censored
7	Treated	24.2667	3.0	24	50.9276	67.3704	-16.4428	Censored
7	Treated	30.2333	3.0	30	46.9686	67.3704	-20.4018	Censored
7	Treated	36.4000	3.0	36	46.7999	67.3704	-20.5705	Censored
7	Treated	42.4667	3.0	42	40.4879	67.3704	-26.8825	Censored
9	Treated	0.0000	1.5	0	27.9338	27.9338	0.0000	ESKD
9	Treated	3.2000	1.5	3	25.6450	27.9338	-2.2887	ESKD

Appendix A.4: List of subjects where Time-to-Dropout < Target Month based on a 1.5 or 3 month window

Obs	*Subject*	*Treatment Group*	*Recorded Month*	*Timing Window*	*Target Month*	*eGFR*	*Baseline eGFR (eGFR0)*	*CFB eGFR*	*Time to Dropout*	*Cause of Dropout*
67	26	Control	46.0000	3	48	70.2120	96.197	-25.9854	46.3717	Censored
72	29	Control	22.9333	3	24	54.9153	81.498	-26.5823	23.6366	Censored
778	294	Control	35.4333	3	36	9.3617	23.289	-13.9277	35.9569	Censored
997	373	Control	28.6333	3	30	38.2007	33.408	4.7928	29.2546	Censored
1106	419	Control	16.1000	3	18	8.1547	30.502	-22.3473	17.5113	ESKD
1217	469	Control	21.7667	3	24	22.6710	37.100	-14.4290	22.6181	Censored
1230	476	Control	22.6333	3	24	38.1734	46.764	-8.5901	23.4723	Censored
1619	596	Control	45.0667	3	48	17.8827	34.001	-16.1183	45.4517	Censored
2706	948	Control	34.3333	3	36	34.9445	44.746	-9.8014	35.8583	Censored
2925	1017	Control	29.1333	3	30	42.7727	75.355	-32.5820	29.7474	Censored
3059	1067	Control	29.3000	3	30	54.4602	72.255	-17.7952	29.9117	Censored
3067	1071	Control	34.2333	3	36	63.7885	64.896	-1.1080	34.7741	Censored
3082	1075	Control	22.8667	3	24	27.6650	32.222	-4.5569	23.5708	Censored
3833	218	Treated	34.9333	3	36	7.5213	21.897	-14.3758	35.8439	ESKD
3896	239	Treated	46.3667	3	48	18.8357	49.274	-30.4383	46.7331	Censored
4323	376	Treated	22.6667	3	24	22.4605	36.765	-14.3050	23.3737	Censored
4439	421	Treated	28.9667	3	30	22.6360	34.480	-11.8443	29.5832	Censored
4502	450	Treated	22.8000	3	24	72.4174	65.970	6.4470	23.5051	Censored
4546	467	Treated	10.9667	3	12	17.4004	45.631	-28.2310	11.8419	Censored
4573	477	Treated	22.4667	3	24	22.4061	58.723	-36.3173	23.1766	Censored
4932	586	Treated	33.8333	3	36	26.5667	39.431	-12.8646	34.3799	Censored
5075	624	Treated	46.8333	3	48	25.8911	63.780	-37.8886	47.1930	Censored
5301	696	Treated	34.7667	3	36	24.1020	44.527	-20.4253	35.2998	Censored
5361	716	Treated	46.2667	3	48	23.1454	43.641	-20.4957	46.6345	Censored
5370	717	Treated	46.0000	3	48	65.5307	100.749	-35.2183	46.3717	Censored
5978	904	Treated	34.7667	3	36	82.7204	94.598	-11.8772	35.2998	Censored
6102	943	Treated	47.1333	3	48	26.7219	62.826	-36.1039	47.4887	Censored
6181	969	Treated	28.9000	3	30	25.9030	46.600	-20.6967	29.5175	Censored
6327	1021	Treated	41.1667	3	42	94.5247	65.811	28.7133	41.6078	Censored
6335	1023	Treated	35.2333	3	36	33.3287	31.997	1.3316	35.7598	Censored
6446	1064	Treated	28.2333	3	30	18.7024	31.696	-12.9936	28.8604	Censored
6602	1133	Treated	22.4000	3	24	61.3881	56.704	4.6845	23.1109	Censored

Appendix B.1: Summary Statistics on eGFR for the IDNT(CNTRL) Study

Trt	*Month*	*N*	*Minimum eGFR*	*Maximum eGFR*	*Mean eGFR*	*Std Dev eGFR*	*Mean Change from Baseline eGFR*	*Std Dev Change from Baseline eGFR*
Control	0	563	16.6028	117.405	50.5469	20.0129	0.0000	0.0000
	3	464	9.9574	117.250	47.6884	20.7035	-2.3866	9.8790
	6	479	8.6896	117.079	45.9531	20.8728	-4.7233	10.6251
	12	442	8.2543	116.634	44.1064	20.9197	-7.1417	11.2865
	18	393	8.1547	129.142	43.3667	21.0605	-9.0445	13.0828
	24	341	9.2974	115.793	42.5288	19.9608	-10.5034	12.5833
	30	239	4.3754	115.545	42.6417	20.4753	-11.0434	12.1977
	36	162	9.3617	102.485	43.3722	19.1259	-12.4836	13.4222
	42	98	12.2567	99.158	42.4804	18.8664	-14.6207	13.7874
	48	49	15.5905	77.603	37.4565	14.5245	-15.8636	13.1808

Trt	*Month*	*N*	*Minimum eGFR*	*Maximum eGFR*	*Mean eGFR*	*Std Dev eGFR*	*Mean Change from Baseline eGFR*	*Std Dev Change from Baseline eGFR*
Treated	0	572	6.3483	106.046	49.8280	18.9838	0.0000	0.0000
	3	472	12.4824	115.159	46.3074	19.3057	-3.9386	10.2595
	6	483	9.2324	104.631	45.4278	19.6116	-5.2984	9.0510
	12	455	9.1961	113.924	43.2194	19.0692	-7.8076	10.9555
	18	404	11.4370	120.540	41.2170	18.7907	-9.7710	11.9196
	24	352	9.9068	97.459	41.2015	18.9335	-11.1089	12.4731
	30	252	8.5977	108.842	41.1397	19.0290	-11.7534	12.1076
	36	184	7.5213	103.074	40.4737	18.6401	-12.5455	13.0431
	42	124	13.2524	108.104	41.3639	20.0237	-14.3812	14.8036
	48	63	10.7093	94.114	40.5604	18.7182	-14.3787	15.7036

Appendix B.2: Summary Statistics on ESKD events, Deaths and Total (ESKD or Death) Events

Trt	*Month*	*N*	*Number of ESKD Events*	*Prop. of ESKD Events*	*Number of Mortality Events*	*Prop. of Mortal Events*	*Number of Total Events*	*Prop. Of ESKD or Death*
Control	0	563	75	0.13321	70	0.12433	134	0.23801
	3	464	66	0.14224	58	0.12500	115	0.24784
	6	479	63	0.13152	49	0.10230	104	0.21712
	12	442	54	0.12217	38	0.08597	86	0.19457
	18	393	34	0.08651	34	0.08651	62	0.15776
	24	341	22	0.06452	24	0.07038	42	0.12317
	30	239	11	0.04603	15	0.06276	23	0.09623
	36	162	7	0.04321	9	0.05556	14	0.08642
	42	98	5	0.05102	2	0.02041	6	0.06122
	48	49	0	0.00000	0	0.00000	0	0.00000

Trt	*Month*	*N*	*Number of ESKD Events*	*Proportion of ESKD Events*	*Number of Mortality Events*	*Proportion of Total Events*	*Number of Total Events*	*Prop. Of ESKD or Death*
Treated	0	572	56	0.09790	68	0.11888	116	0.20280
	3	472	44	0.09322	47	0.09958	86	0.18220
	6	483	42	0.08696	49	0.10145	84	0.17391
	12	455	27	0.05934	37	0.08132	60	0.13187
	18	404	24	0.05941	27	0.06683	48	0.11881
	24	352	15	0.04261	16	0.04545	29	0.08239
	30	252	13	0.05159	10	0.03968	22	0.08730
	36	184	7	0.03804	7	0.03804	13	0.07065
	42	124	3	0.02419	5	0.04032	7	0.05645
	48	63	1	0.01587	3	0.04762	3	0.04762