Longitudinal Models in FACTS

Presented By: Nick Berry
Senior Statistical Scientist
Berry Consultants
April 25, 2025

BERRY

Let’s Set Up an Example Trial:

- **Indication**: Early Onset Alzheimer's Disease
- **Endpoint**: Change from Baseline in ADCOMS at 52 weeks
  - Composite endpoint measuring cognitive impairment
  - Lower values of ADCOMS are good
  - 0 means no CFB, but we expect subjects to decline. Looking to minimize decline.
- **Treatments**: 5 different treatment arms
  - Cross (2.5, 5, 10)x(biweekly, monthly) and leave out 2.5 mg/kg monthly
- **Expected Response:** Expect control to worsen by about 0.1. Would love to have an active arm worsen by no more than 0.075. Call 0.025 clinically significant (CSD).
- **Accrual Rate** of 3 patients per month on average
- **Adaptations**: Want to detect clinically significant improvement in any dose.
  - Many interim analyses – stop if Pr(CSD) > 0.95

Let’s Set Up an Example Trial:

- **Indication**: Early Onset Alzheimer's Disease
- **Endpoint**: Change from Baseline in ADCOMS at 52 weeks
  - Composite endpoint measuring cognitive impairment
  - Lower values of ADCOMS are good
  - 0 means no CFB, but we expect subjects to decline. Looking to minimize decline.
- **Treatments**
  - Cross (2
- **Expected**
  active arm
- **Adaptatio**
  - Many inte

ave an
SD).

We’re mimicking a lot of the Ban2401/lecanemab Phase 2 study design, but with some simplifications:

- Not using Response Adaptive Randomization
- Not using 2D NDLM to model dose response
- Leaving out some interim analyses
- Not calculating ED90 for dose selection
- Some adaptive rules are different

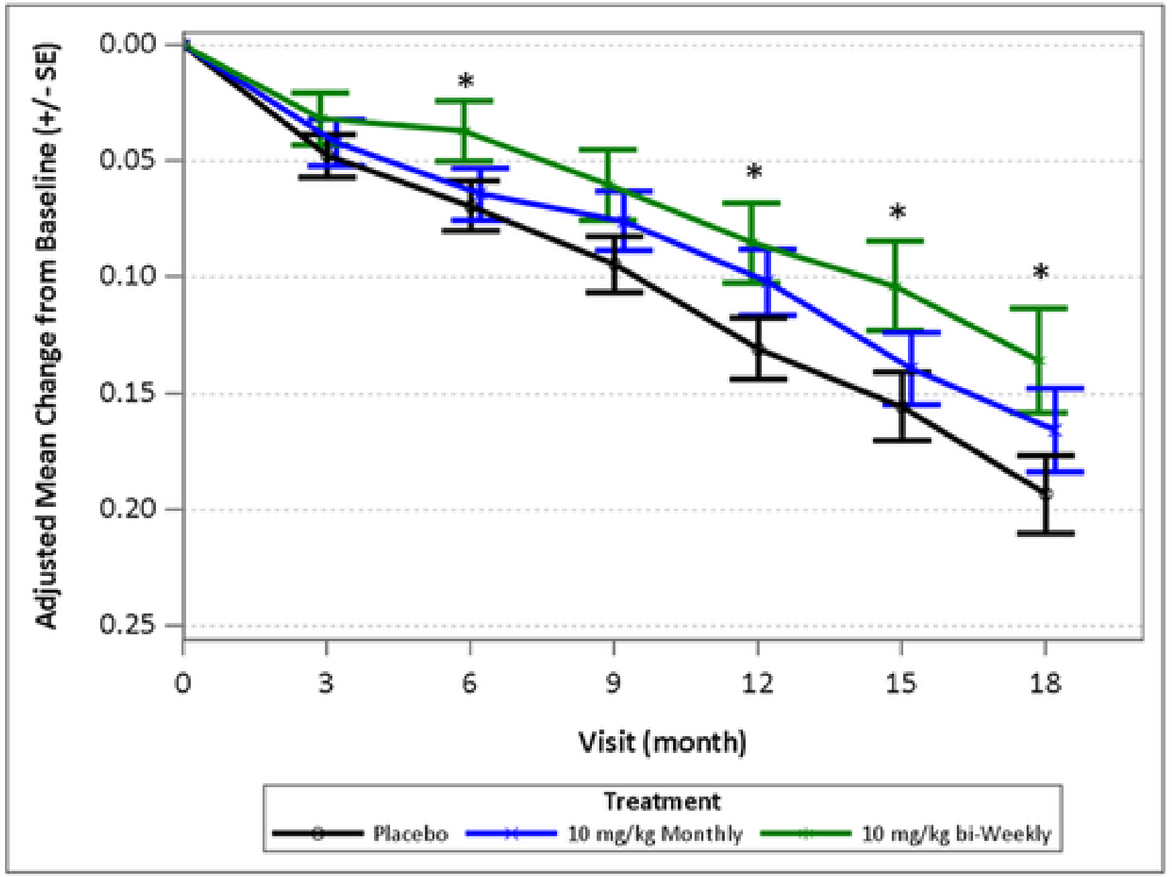
BERRY

Jump to FACTS to set up study

BERRY

Endpoint Simulation Based on Reality

A



N (ADCOMS)	0 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Placebo	238	226	216	201	187	172	160
10 mg/kg monthly	246	235	208	177	165	152	146
10 mg/kg biweekly	152	143	130	105	93	89	79

BERRY

From Ban2401/lecanemab Phase 2 study: https://alzres.biomedcentral.com/articles/10.1186/s13195-021-00813-8

Notes about preliminary simulations:

- Only about 6 patients complete/arm at the first interim analysis (200 enrolled)

- 32-33 subjects complete/arm at the 4th interim analysis (350 enrolled)
- Standard error for estimate of the treatment mean is about:

  0.18/sqrt(32.333) = 0.032

- There's an obvious improvement to be had here. We have 3, 6, and 9 months data – lets use it.

BERRY

Longitudinal Modeling in FACTS

- What kind of longitudinal model are we using?
  - Longitudinal modeling in FACTS is done through multiple imputation.
  - Longitudinal models in FACTS are not MMRMs or disease progression joint models.

- The multiple imputation model works seamlessly with the Bayesian model
  - Longitudinal models are only available for the Bayesian model in FACTS
  - The result is an estimate of the final endpoint response that uses intermediate endpoint data
  - Completely meshes, and is co-estimated, with the specified dose response model

- Longitudinal models are always used to impute subjects who are in follow-up but do not have complete data.
  - They may or may not be used to impute subjects who drop out of study (user choice)

- Longitudinal models in FACTS improve estimation when there is missing data to be imputed. They do not change estimation if all subjects have complete data.

Longitudinal Modeling in FACTS

# Subject	DateInWeeks	Dose	Visit 1	Visit 2	Visit 3	Visit 4
1	0.110473	6	0.138093	0.049056	0.121192	0.124474
2	0.605416	1	0.234711	0.099914	0.082771	0.111682
3	0.627071	2	0.326255	0.29067	0.178798	0.142401
4	0.654148	3	0.166945	0.007714	0.381218	0.49103
			•			
			•			
			•			
191	62.869809	2	-0.305708	-0.041229	-0.148199	-9999
192	62.939216	1	-0.142279	-0.25435	-0.114264	-9999
193	62.998279	4	0.256003	0.037889	0.135714	-9999
194	63.619419	1	0.318195	0.321106	0.212852	-9999
195	63.813769	5	-0.131625	-0.300807	-0.365334	-9999
			•			
			•			
			•			
234	74.681472	6	0.028898	0.228168	-9999	-9999
235	74.810279	4	-0.042367	-0.259138	-9999	-9999
236	75.084673	1	0.064986	0.202237	-9999	-9999
237	75.533525	3	-0.0979	0.106645	-9999	-9999
238	75.604488	6	0.15441	0.199379	-9999	-9999
			•			
			•			
			•			
266	87.698776	5	0.108183	-9999	-9999	-9999
267	88.244401	4	-0.327898	-9999	-9999	-9999
268	88.374474	1	-0.085789	-9999	-9999	-9999
269	88.558466	2	-0.01254	-9999	-9999	-9999
270	88.710088	6	0.024023	-9999	-9999	-9999
			•			
			•			
			•			
303	100.599505	1	-9999	-9999	-9999	-9999
304	100.76764	2	-9999	-9999	-9999	-9999
305	100.882624	5	-9999	-9999	-9999	-9999
306	100.901354	4	-9999	-9999	-9999	-9999
307	101.402645	2	-9999	-9999	-9999	-9999

These subjects have complete data. They are used to estimate the imputation model(s).

Longitudinal Modeling in FACTS

# Subject	DateInWeeks	Dose	Visit 1	Visit 2	Visit 3	Visit 4
1	0.110473	6	0.138093	0.049056	0.121192	0.124474
2	0.605416	1	0.234711	0.099914	0.082771	0.111682
3	0.627071	2	0.326255	0.29067	0.178798	0.142401
4	0.654148	3	0.166945	0.007714	0.381218	0.49103
			•			
			•			
			•			
191	62.869809	2	-0.305708	-0.041229	-0.148199	-9999
192	62.939216	1	-0.142279	-0.25435	-0.114264	-9999
193	62.998279	4	0.256003	0.037889	0.135714	-9999
194	63.619419	1	0.318195	0.321106	0.212852	-9999
195	63.813769	5	-0.131625	-0.300807	-0.365334	-9999
			•			
			•			
			•			
234	74.681472	6	0.028898	0.228168	-9999	-9999
235	74.810279	4	-0.042367	-0.259138	-9999	-9999
236	75.084673	1	0.064986	0.202237	-9999	-9999
237	75.533525	3	-0.0979	0.106645	-9999	-9999
238	75.604488	6	0.15441	0.199379	-9999	-9999
			•			
			•			
			•			
266	87.698776	5	0.108183	-9999	-9999	-9999
267	88.244401	4	-0.327898	-9999	-9999	-9999
268	88.374474	1	-0.085789	-9999	-9999	-9999
269	88.558466	2	-0.01254	-9999	-9999	-9999
270	88.710088	6	0.024023	-9999	-9999	-9999
			•			
			•			
			•			
303	100.599505	1	-9999	-9999	-9999	-9999
304	100.76764	2	-9999	-9999	-9999	-9999
305	100.882624	5	-9999	-9999	-9999	-9999
306	100.901354	4	-9999	-9999	-9999	-9999
307	101.402645	2	-9999	-9999	-9999	-9999

← These subjects have complete data. They are used to estimate the imputation model(s).

← These subjects have their 12M data imputed based on 3mo, 6mo, & 9mo data.

Longitudinal Modeling in FACTS

# Subject	DateInWeeks	Dose	Visit 1	Visit 2	Visit 3	Visit 4
1	0.110473	6	0.138093	0.049056	0.121192	0.124474
2	0.605416	1	0.234711	0.099914	0.082771	0.111682
3	0.627071	2	0.326255	0.29067	0.178798	0.142401
4	0.654148	3	0.166945	0.007714	0.381218	0.49103
⋮						
191	62.869809	2	-0.305708	-0.041229	-0.148199	-9999
192	62.939216	1	-0.142279	-0.25435	-0.114264	-9999
193	62.998279	4	0.256003	0.037889	0.135714	-9999
194	63.619419	1	0.318195	0.321106	0.212852	-9999
195	63.813769	5	-0.131625	-0.300807	-0.365334	-9999
⋮						
234	74.681472	6	0.028898	0.228168	-9999	-9999
235	74.810279	4	-0.042367	-0.259138	-9999	-9999
236	75.084673	1	0.064986	0.202237	-9999	-9999
237	75.533525	3	-0.0979	0.106645	-9999	-9999
238	75.604488	6	0.15441	0.199379	-9999	-9999
⋮						
266	87.698776	5	0.108183	-9999	-9999	-9999
267	88.244401	4	-0.327898	-9999	-9999	-9999
268	88.374474	1	-0.085789	-9999	-9999	-9999
269	88.558466	2	-0.01254	-9999	-9999	-9999
270	88.710088	6	0.024023	-9999	-9999	-9999
⋮						
303	100.599505	1	-9999	-9999	-9999	-9999
304	100.76764	2	-9999	-9999	-9999	-9999
305	100.882624	5	-9999	-9999	-9999	-9999
306	100.901354	4	-9999	-9999	-9999	-9999
307	101.402645	2	-9999	-9999	-9999	-9999

← These subjects have complete data. They are used to estimate the imputation model(s).

← These subjects have their 12M data imputed based on 3mo, 6mo, & 9mo data.

← These subjects have their 12M data imputed based on 3mo and 6mo data.

Longitudinal Modeling in FACTS

# Subject	DateInWeeks	Dose	Visit 1	Visit 2	Visit 3	Visit 4
1	0.110473	6	0.138093	0.049056	0.121192	0.124474
2	0.605416	1	0.234711	0.099914	0.082771	0.111682
3	0.627071	2	0.326255	0.29067	0.178798	0.142401
4	0.654148	3	0.166945	0.007714	0.381218	0.49103
⋮						
191	62.869809	2	-0.305708	-0.041229	-0.148199	-9999
192	62.939216	1	-0.142279	-0.25435	-0.114264	-9999
193	62.998279	4	0.256003	0.037889	0.135714	-9999
194	63.619419	1	0.318195	0.321106	0.212852	-9999
195	63.813769	5	-0.131625	-0.300807	-0.365334	-9999
⋮						
234	74.681472	6	0.028898	0.228168	-9999	-9999
235	74.810279	4	-0.042367	-0.259138	-9999	-9999
236	75.084673	1	0.064986	0.202237	-9999	-9999
237	75.533525	3	-0.0979	0.106645	-9999	-9999
238	75.604488	6	0.15441	0.199379	-9999	-9999
⋮						
266	87.698776	5	0.108183	-9999	-9999	-9999
267	88.244401	4	-0.327898	-9999	-9999	-9999
268	88.374474	1	-0.085789	-9999	-9999	-9999
269	88.558466	2	-0.01254	-9999	-9999	-9999
270	88.710088	6	0.024023	-9999	-9999	-9999
⋮						
303	100.599505	1	-9999	-9999	-9999	-9999
304	100.76764	2	-9999	-9999	-9999	-9999
305	100.882624	5	-9999	-9999	-9999	-9999
306	100.901354	4	-9999	-9999	-9999	-9999
307	101.402645	2	-9999	-9999	-9999	-9999

← These subjects have complete data. They are used to estimate the imputation model(s).

← These subjects have their 12M data imputed based on 3mo, 6mo, & 9mo data.

← These subjects have their 12M data imputed based on 3mo and 6mo data.

← These subjects have their 12M data imputed based on 3mo data.

Longitudinal Modeling in FACTS

# Subject	DateInWeeks	Dose	Visit 1	Visit 2	Visit 3	Visit 4
1	0.110473	6	0.138093	0.049056	0.121192	0.124474
2	0.605416	1	0.234711	0.099914	0.082771	0.111682
3	0.627071	2	0.326255	0.29067	0.178798	0.142401
4	0.654148	3	0.166945	0.007714	0.381218	0.49103
⋮						
191	62.869809	2	-0.305708	-0.041229	-0.148199	-9999
192	62.939216	1	-0.142279	-0.25435	-0.114264	-9999
193	62.998279	4	0.256003	0.037889	0.135714	-9999
194	63.619419	1	0.318195	0.321106	0.212852	-9999
195	63.813769	5	-0.131625	-0.300807	-0.365334	-9999
⋮						
234	74.681472	6	0.028898	0.228168	-9999	-9999
235	74.810279	4	-0.042367	-0.259138	-9999	-9999
236	75.084673	1	0.064986	0.202237	-9999	-9999
237	75.533525	3	-0.0979	0.106645	-9999	-9999
238	75.604488	6	0.15441	0.199379	-9999	-9999
⋮						
266	87.698776	5	0.108183	-9999	-9999	-9999
267	88.244401	4	-0.327898	-9999	-9999	-9999
268	88.374474	1	-0.085789	-9999	-9999	-9999
269	88.558466	2	-0.01254	-9999	-9999	-9999
270	88.710088	6	0.024023	-9999	-9999	-9999
⋮						
303	100.599505	1	-9999	-9999	-9999	-9999
304	100.76764	2	-9999	-9999	-9999	-9999
305	100.882624	5	-9999	-9999	-9999	-9999
306	100.901354	4	-9999	-9999	-9999	-9999
307	101.402645	2	-9999	-9999	-9999	-9999

← These subjects have complete data. They are used to estimate the imputation model(s).

← These subjects have their 12M data imputed based on 3mo, 6mo, & 9mo data.

← These subjects have their 12M data imputed based on 3mo and 6mo data.

← These subjects have their 12M data imputed based on 3mo data.

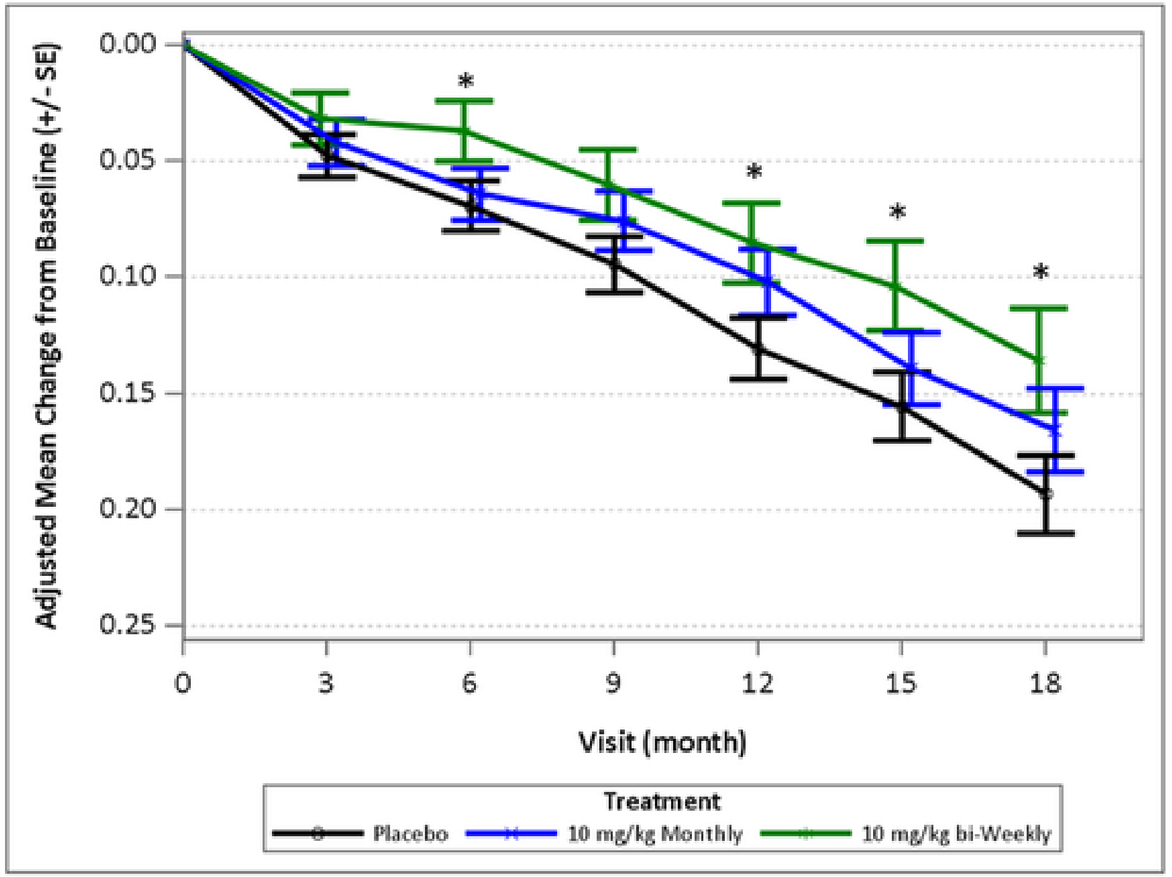
← These subjects have no intermediate data. They cannot be imputed except for naively.

Let’s set this up in FACTS

BERRY

Endpoint Simulation Based on Reality

A



N (ADCOMS)	0 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Placebo	238	226	216	201	187	172	160
10 mg/kg monthly	246	235	208	177	165	152	146
10 mg/kg biweekly	152	143	130	105	93	89	79

BERRY

From Ban2401/lecanemab Phase 2 study: https://alzres.biomedcentral.com/articles/10.1186/s13195-021-00813-8

Have we gained anything with the LM?

- Going back to the 4th interim analysis.
  - We still expect 194 subjects with complete data (>12 months of follow-up) on average
  - We also have an expectation of:
    - 39 subjects with between 9 and 12 months of follow-up
    - 39 subjects with between 6 and 9 months of follow-up
    - 39 subjects with between 3 and 6 months of follow-up
    - 39 subjects with less than 3 months of follow-up

These subjects give us information!

Have we gained anything with the LM?

Model	SE of Estimate of Control (ESS [+LMgain])	SE of Estimate of 10 mg/kg biweekly dose (ESS [+LMgain])	Total Number Complete	Total ESS
No longitudinal data	0.0317	0.0317		
Using LM with no endpoint correlation	0.0310	0.0300		
Using LM with weak endpoint correlation	0.0295	0.0287		
Using LM with strong endpoint correlation	0.0271	0.0266		

ESS = Effective Sample Size
LMgain = Gain in ESS over the no longitudinal data model.

Have we gained anything with the LM?

Model	SE of Estimate of Control (ESS [+LMgain])	SE of Estimate of 10 mg/kg biweekly dose (ESS [+LMgain])	Total Number Complete	Total ESS
No longitudinal data	0.0317 (32.2)	0.0317 (32.2)		
Using LM with no endpoint correlation	0.0310 (33.7 [+1.5])	0.0300 (35.9 [+3.7])		
Using LM with weak endpoint correlation	0.0295 (37.2 [+5])	0.0287 (39.4 [+7.2])		
Using LM with strong endpoint correlation	0.0271 (44.2 [+12])	0.0266 (45.8 [+13.6])		

ESS = Effective Sample Size
LMgain = Gain in ESS over the no longitudinal data model.

BERRY

Have we gained anything with the LM?

Model	SE of Estimate of Control (ESS [+LMgain])	SE of Estimate of 10 mg/kg biweekly dose (ESS [+LMgain])	Total Number Complete	Total ESS
No longitudinal data	0.0317 (32.2)	0.0317 (32.2)	194	194
Using LM with no endpoint correlation	0.0310 (33.7 [+1.5])	0.0300 (35.9 [+3.7])	194	213.3 (+19.3)
Using LM with weak endpoint correlation	0.0295 (37.2 [+5])	0.0287 (39.4 [+7.2])	194	234.2 (+40.2)
Using LM with strong endpoint correlation	0.0271 (44.2 [+12])	0.0266 (45.8 [+13.6])	194	273.2 (+79.2)

ESS = Effective Sample Size
LMgain = Gain in ESS over the no longitudinal data model.

Have we gained anything with the LM?

Model	SE of Estimate of Control (ESS [+LMgain])	SE of Estimate of 10 mg/kg biweekly dose (ESS [+LMgain])	Total Number Complete	Total ESS
No longitudinal data	0.0317 (32.2)	0.0317 (32.2)	194	194
Using LM with no endpoint correlation	0.0310 (33.7 [+1.5])	0.0300 (35.9 [+3.7])	194	213.3 (+19.3)
Using LM with weak endpoint correlation	0.0295 (37.2 [+5])	0.0287 (39.4 [+7.2])	194	234.2 (+40.2)
Using LM with strong endpoint correlation	0.0271 (44.2 [+12])	0.0266 (45.8 [+13.6])	194	273.2 (+79.2)

ESS = Effective Sample Size
LMgain = Gain in ESS over the no longitudinal data model.

Best possible gain (perfect longitudinal correlation) is an ESS of 311

Gains from LM across different numbers of LM models

Average SE of estimated treatment response estimate

Simulation Method	Each Arm Has Own Model	Control has its own and treatments share 1 model	All arms share the same model
No longitudinal data	0.0317		
Using LM with no endpoint correlation	0.032	0.0300	0.0298
Using LM with weak endpoint correlation	0.031	0.0287	0.0285
Using LM with strong endpoint correlation	0.028	0.0266	0.0265

Okay, cool. But, do these changes result in improvements in operating characteristics?

BERRY

Operating Characteristic Changes

Comparing operating characteristics of the trial with no longitudinal data vs. varying degrees of longitudinal correlation to go along with the “Model Control Separately” set of longitudinal models.

Key:
POWER
(Mean N)

Scenario	No Longitudinal Data	Use Longitudinal Model, but data not correlated	Use Longitudinal Model, and data has weak correlation	Use Longitudinal Model, and data has strong correlation
Null	**0.081** 711	**0.081** 647	**0.082** 673	**0.076** 692
All Doses are okay	**0.28** 716	**0.29** 666	**0.28** 679	**0.28** 699
All doses are good	**0.66** 649	**0.63** 614	**0.67** 609	**0.67** 607
All doses are great	**0.93** 535	**0.92** 512	**0.91** 505	**0.94** 466
Doses linearly improve	**0.60** 668	**0.59** 633	**0.62** 629	**0.61** 632
Low doses not good, but gets good for high	**0.69** 649	**0.67** 624	**0.69** 622	**0.72** 607
Similar to Lecanemab S2 results	**0.34** 710	**0.308** 661	**0.342** 675	**0.338** 693

Operating Characteristic Changes

Comparing operating characteristics of the trial with no longitudinal data vs. varying degrees of longitudinal correlation to go along with the “Model Control Separately” set of longitudinal models.

Key:
POWER
(Mean N)

Scenario	No Longitudinal Data	Use Longitudinal Model, but data not correlated	Use Longitudinal Model, and data has weak correlation	Use Longitudinal Model, and data has strong correlation
Null	**0.081** 711	**0.081** 647	**0.082** 673	**0.076** 692
All Doses are okay	**0.2** 71			**0.28** 699
All doses are good	**0.6** 64			**0.67** 607
All doses are great	**0.9** 53			**0.94** 466
Doses linearly improve	**0.60** 668	**0.59** 633	**0.62** 629	**0.61** 632
Low doses not good, but gets good for high	**0.69** 649	**0.67** 624	**0.69** 622	**0.72** 607
Similar to Lecanemab S2 results	**0.34** 710	**0.308** 661	**0.342** 675	**0.338** 693

To get the Type I errors to match I had to make the interim boundaries for the “No longitudinal data” model more conservative.

The Type I error was considerably higher in that trial than the trials with longitudinal imputation.

Summary

- There are many options for longitudinal models, aka multiple imputation models, in FACTS.
  - We sort of scratched the surface here, but there is much more to investigate (we never talked about predictive probabilities and how longitudinal models can improve those predictions, for example)

- When decisions are being made without complete information, including a multiple imputation model can improves efficiency.

- Efficiency gains largely depend on the amount of correlation between early and final endpoints in the data.

- Interim analysis models have smaller credible intervals around response estimates when using longitudinal imputation models. It’s not a small improvement.

BERRY