



WORKED EXAMPLE

Effect of Neladenoson
Bialanate on Exercise
Capacity Among Patients
with Heart Failure with
Preserved Ejection Fraction:
A Randomized Clinical Trial.



Title: Effect of Neladenoson Bialanate on Exercise Capacity Among Patients with Heart Failure with Preserved Ejection Fraction: A Randomized Clinical Trial.

Objective: To determine whether neladenoson improves exercise capacity, physical activity, cardiac biomarkers, and quality of life in patients with HFpEF and to find the optimal dose.

Year: 2019

Source: Journal of the American Medical Association

Link: <https://doi.org/10.1001/jama.2019.6717>

Protocol: <https://clinicaltrials.gov/ct2/show/NCT03098979>

Clinical Area: Cardiology

Sample Size Section in Paper/Protocol:

“Based on the assumption of a maximum effect for an absolute increase in 6-minute walk test distance of **40 m for a particular dose** of neladenoson bialanate, an absolute increase of **0 m with placebo**, and an **SD of 80 m**, an **overall sample size of 216** randomized patients (using a **1:2:2:2:3 randomization ratio** corresponding to the 5 neladenoson doses and placebo) was required to ensure a **minimum power of 80%** to detect the presence of a dose response.”

“Patients (were) randomized to receive neladenoson (**5 mg, 10 mg, 20 mg, 30 mg, or 40 mg**) or placebo”

“A multiple comparison procedure with 5 modelling techniques (**linear, Emax, 2 variations of sigmoidal Emax, and quadratic**) was used to evaluate diverse dose-response profiles.”

“All statistical tests were performed at a **significance level of .05**. Significance testing was **1-sided**.”



Summary of Necessary Parameter Estimates for Sample Size Calculation

Parameter	Value
Significance Level (1-sided)	0.05
Number of Doses	6 (0mg, 5mg, 10mg, 20mg, 30mg, 40mg)
Sample Size Ratio per Dose	3:1:2:2:2:2
Number of Models	5 (Linear, Emax, Sigmoid Emax (x2), Quadratic)
Power Criterion	Minimum
Placebo Effect, δ_0	0
Max Treatment Effect, δ_1	40
Standard Deviation, σ	80
Power	80%

Parameter Values for Dose-Response Models

Model (Table 10-1 in Clinical Study Protocol)	Parameter Values
Linear: $f(d) = d$	No input required
Emax: $f(d) = \frac{41.25d}{1.25+d}$	$\theta_1 = 1.25$
Sigmoid Emax 1: $f(d) = \frac{40.1d^4}{9^4+d^4}$	$\theta_1 = 9, \theta_2 = 4$
Sigmoid Emax 2: $f(d) = \frac{45d^3}{20^3+d^3}$	$\theta_1 = 20, \theta_2 = 3$
Quadratic: $f(d) = 2.667d - 0.044d^2$	$\theta_1 = -0.044/2.667$



Step 1:

Select the **MGT5 Multiple Comparisons Procedure - Modelling for Continuous Outcome (Common Variance) (MCP-Mod)** table from the Study Design Pane.

This can be done **using the radio buttons** or alternatively, you can **use the search bar** at the end of the Select Test Design & Goal window.

Design	Goals	No. of Groups	Analysis Methods
<input type="checkbox"/> Fixed	<input checked="" type="checkbox"/> Means	<input type="checkbox"/> One Group	<input checked="" type="checkbox"/> Inequality
<input type="checkbox"/> Bayesian	<input type="checkbox"/> Proportions	<input type="checkbox"/> Paired	<input type="checkbox"/> Equivalence
<input checked="" type="checkbox"/> Adaptive	<input type="checkbox"/> Survival	<input type="checkbox"/> Cross-over	<input type="checkbox"/> Non-inferiority
	<input type="checkbox"/> Counts	<input type="checkbox"/> Two	<input type="checkbox"/> Intervals
	<input type="checkbox"/> Agreement	<input checked="" type="checkbox"/> > 2	
	<input type="checkbox"/> Regression	<input type="checkbox"/> Hierarchical	

MGT5	Multiple Comparisons Procedure - Modelling for Continuous Outcome (Common Variance) (MCP-Mod)
MGT6	Multiple Arms Multiple Stage (MaMs) Group Sequential Design for Means
MGT7	Multiple Comparisons Procedure - Modelling for Poisson Rates (MCP-Mod)
MGT8	Multiple Comparisons Procedure - Modelling for Negative Binomial Rates (MCP-Mod)

Type here to search all tests... Clear Search

OK Cancel

Step 2:

Enter the parameter values in the main table for the sample size calculation taken from the study description.

First, complete the **main table**. Note: Minimum power criterion implies that the total power of the test will be equal to the minimum power of the candidate models.

An optional random seed is also specified here to allow replicable results.



	1	2	3
Test Significance Level, α	0.100		
1 or 2 Sided Test?	2	2	2
Number of Doses, D	5		
Number of Models, M	4		
Power Criterion	Mean	Mean	Mean
Placebo Effect, δ_0	0.000		
Max Treatment Effect, δ_1	1.000		
Standard Deviation, σ	0.100		
Power (%)			
Critical Value, T_{α}			
Random Seed	9876		
Total Sample Size, N			

Next, complete the Dose Levels and Candidate Models **side table**. The weighting is used to distribute the sample size across the dose groups as specified.

	Dose	Weighting	σ	Model	1	2	3	4	5
1	0.000	1.000		Linear					
2	5.000	1.000		Emax (20%)	1.250	0.000	20.000		-0.0446767
3	10.000	2.000		Sigmoid Emax (20%)	4.000	3.000			
4	20.000	2.000		Sigmoid Emax (20%)					
5	30.000	2.000		Quadratic (2)					
6	40.000	2.000		Quadratic (2)					
				Model Power					
				Placebo Dose, δ_0	0.000	0.000	0.000	0.000	0.000
				Max Effect Dose, δ_1	40.000	40.000	40.000	40.000	40.000
				σ					
				Emax					

Step 3:

Enter the required **power** in the main table and the **sample size** and **candidate model powers** will be calculated.

The analysis calculates a total sample size of 216 with 54 subjects in the placebo group, 18 subjects in the 5mg dose group and 36 subjects in each of the remaining dose groups.

A minimum power of 80.31% was achieved with this sample size. The per-model powers ranged from 80.31% (Sigmoid Emax model with parameters 20 & 3) to 91.79% (Sigmoid Emax model with parameters 9 & 4).

The maximum effect dose was the 40mg dose for the Linear, Emax and Sigmoid Emax models while the Quadratic model achieved the maximum effect at the 30mg dose.

This sample size is consistent with the source paper.



MCT5-1 / Multiple Comparisons Procedure - Modelling for Continuous Outcome (Common Variance) (MCP-Mod)										
	1	2	3	4	5	6	7	8	9	10
Test Significance Level, α	0.050									
1 or 2 Sided Test?	1	1	1	1	1	1	1	1	1	1
Number of Doses, D	6									
Number of Models, M	5									
Power Criterion	Minimum	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Placebo Effect, μ_0	0.000									
Max Treatment Effect, μ_1	40.000									
Standard Deviation, σ	80.000									
Power (%)	88.81									
Total Sample Size, N	216									
Critical Value, T_c	1.958									
Random Seed	4021									

MCT55-1 Plot Dose Response										
Doses	Weighting	n	Model	1	2	3	4	5		
1	0.000	1.000	54.000	Linear	Emax (ED50)	Sigmoid Emax (ED50, h)	Sigmoid Emax (ED50, h)	Quadratic (δ)		
2	1.000	1.000	18.000	1.000	1.250	9.000	20.000	-0.016		
3	10.000	1.000	36.000	Parameter 1, β_1	Parameter 2, β_2	Parameter 3, β_3	Parameter 4, β_4	2.842		
4	20.000	1.000	36.000	Parameter 5, β_5				-0.044		
5	30.000	1.000	36.000	Model Power	81.07%	88.81%	91.79%	80.31%		
6	40.000	1.000	36.000	Placebo Dose, μ_0	0.000	0.000	0.000	0.000		
				Max Effect Dose, μ_1	40.000	40.000	40.000	40.000		
				SD	0.000	0.000	0.000	0.000		
				Emax		41.250	40.000	40.010		

Output Statement:

"A total sample size of 216 is required to ensure a minimum power of 80.31% for an MCP-Mod analysis rejecting the null hypothesis of no difference between doses using the multiple comparisons procedure (MCP) assuming a placebo dose-response effect of 0, a maximum dose-response effect (in the dose range) of 40 and a common (residual) standard deviation of 80 per dose and one-sided family-wise error rate of 0.05, corresponding to critical multivariate t-statistic of 1.958.

This analysis assumed 6 doses with the following sample sizes per dose:

Doses: 0, 5, 10, 20, 30, 40

Sample Size: 54, 18, 36, 36, 36, 36

The following 5 models (including input parameters) were evaluated in this MCP-Mod analysis and found to have the following per-model power:

Linear: 81.07%

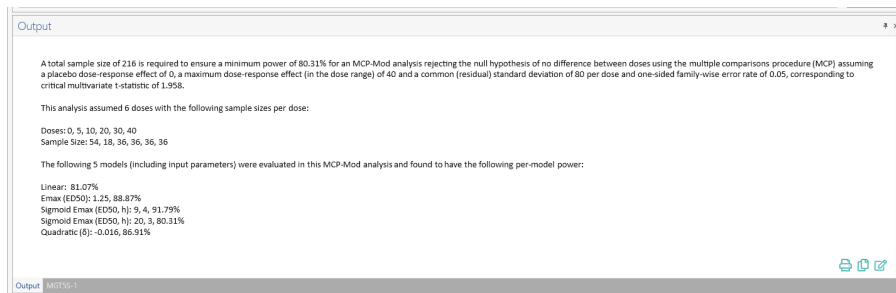
Emax (ED50): 1.25, 88.87%

Sigmoid Emax (ED50, h): 9, 4, 91.79%

Sigmoid Emax (ED50, h): 20, 3, 80.31%

Quadratic (δ): -0.016, 86.91%"

The output statement appears at the bottom of nQuery. This can be printed or copy and pasted into any document.



How the output statement appears in nQuery.

Step 4:

nQuery can also be used to plot the dose responses for each model. To generate these plots, click on the “Plot Dose Responses” button on top of the side table.

