Table 1

STABLE Subjects, defined by SCR-to-BL SARA within 1 point[#]

Stable baseline defined as Total SARA scores at screening and baseline within the group median of 1 point, comprising 63 subjects (69% of total sample)

	BHV-4157	Placebo	Δ Between [95% CI]	Response Definition	BHV-4157	Placebo	*p value
Total SARA STABLE	-0.97 (n=34)	-0.50 (n=29)	-0.39 [-1.2 – 0.45]	≥ 3 points	24%	3.4%	0.08
Total SARA UNSTABLE	-0.67 (n=28)	-1.49 (n=38)	0.62 [-0.01 – 1.82]	≥ 1 point	50%	41%	0.21

*p value from t-test without correction for multiple comparisons

	STABLE		NOT-STABLE	
	BHV-4157 (n=33)	Placebo (n=26)	BHV-4157 (n=28)	Placebo (n=38)
Total SARA	-0.90	-0.50	-0.87	-1.49
Axial SARA (#1 - 4)	-0.27	0.18	-0.46	-0.43
Appendicular SARA (#5-8)	-0.33	-0.84	-0.15	-0.69

#, ≤ 1 point on Total SARA score 1

Table 2

Population selected based on Experience of Site/Raters

Sites selected on the basis that the Principal Investigator has over two decades of ataxia research and PIs are raters, represents 72 subjects (8.9% of total sample)

	BHV-4157 (n=37)	Placebo (n=35)	Δ Btw Groups (95% CI)
Total SARA	-1.37	-0.97	-0.40 [-1.3 – 0.52]
Gait [#3]	-0.14	-0.06	-0.08 [-0.29 – 0.14]
Axial Items [#1 – 4]	-0.47	0.05	-0.52 [-1.1 – 0.07]
Appendicular [#5 – 8]	-0.52	-0.68	0.16 [-0.39 – 0.72]

*, analytic model identical to primary, presenting LSMeans

Response Definition	BHV-4157	Placebo	*p-value
≥ 3 points	21.6%	5.7%	0.03
≥ 1 point	51.4%	31.4%	0.10

*, fisher exact test without correction for multiple comparisons

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Table 3

Population selected based on Experience of Site/Raters

	BHV-4157 (n=37)	Placebo (n=35)	Δ Btw Groups [95% CI]
Total SARA	-1.37	-0.97	-0.40 [-1.3 – 0.52]
Gait [#1]	-0.14	-0.03	-0.08 [-0.29 – 0.14]
Axial Items [#1 – 4]	-0.47	0.05	-0.52 [-1.1 – 0.07]
Appendicular [#5 – 8]	0.52	-0.66	0.16 [-0.39 – 0.72]

**, analysis model identical to primary assessing Ataxias*

- **Assuming true difference from data shown, 500 subjects per arm would be required to provide 90% power for a randomized controlled trial**
  - A study this large is prohibitive for orphan indication and presents challenges detecting signals at 8-weeks
  - Placebo effects may extinguish over long-term
  - Longitudinal cohort can be compared to Natural History Cohort to demonstrate neuroprotective effects

Table 4

Exposure Proxy: Weight (lighter)

- Sample divided by median weight (≤76.4 kg vs >76.4 kg)
- Lighter median had crude preliminary estimate of 20% greater exposure (using unmodeled data) and Phase 1 studies show correlation of weight with exposure

Lighter median	BMN-4157 (n=27)	Placebo (n=39)	Adj Mean Groups (95% CI)
Total SARA*	-1.38	-0.89	-0.50 [-1.0 – 0.00]
Axial items (1 – 4)	-0.95	-0.49	
Appendicular items (5 - 8)	-0.59	-0.46	

	Change in Total SARA Score			Responder Analysis			
Efficacy Sample	BMN-4157	Placebo	Δ SARA (95% CI)	Response Definition	BMN-4157	Placebo	P-value*
All Lighter Subjects	-1.38 (n=27)	-0.89 (n=39)	-0.50 [-1.0 – 0.00]	≥ 2 point Δ SARA Subjects (n=66)	33%	18%	0.24
STASIS Subgroup	-1.28 (n=19)	-0.85 (n=17)	-0.93	≥ 3 point Δ Upper extremities (n=36)	26%	0	0.05
EXP Sites	-1.69 (n=18)	-0.82 (n=19)	-1.09	≥ 3 points in Stable Subjects (n=61)	39%	5%	0.02

** fisher exact test without correction for multiple comparisons*

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Table 5

Exposure Proxy: Weight

- Examination of PGIC and CGI – no correlation or trend in general population or general subpopulations
- Trends in lighter weight sample (from total subset and among experienced sites)

CGI	Sample	BHV-3157	Placebo
Any improvement	lighter	68% (n=32)	45% (n=29)
Much improved	"	27%	7%
Any improvement	lighter at EXP sites	60% (n=35)	33% (n=12)
Much improved	"	34%	8%

PGI	Sample	BHV-3157	Placebo
Any improvement	lighter	84% (n=31)	55% (n=29)
"Better and Definite improvement that has made a real & noticeable difference"	"	37%	0
Any improvement	lighter at EXP sites	85% (n=26)	8% (n=12)
Better and Definite	"	37%	0

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Table 6

Gender as proxy for Exposure

- Females have greater may have approximately 50% greater exposure based on Phase 1 data (c/w Hiltek USPI)

	Change in Total SARA Score		Responder Analysis		
Females	BHV-4157	Placebo	Response Definition	BHV-4157	Placebo
All Subjects	-1.08 (n=31)	-0.82 (n=36)	≥ 3 points in All Subjects (n=67)	32%	17%
STAIR Subgroup	-1.33 (n=15)	-0.40 (n=15)	≥ 3 points at Experienced sites (n=32)	19%	0
Experience of Sites	-1.15 (n=20)	-0.61 (n=18)	≥ 3 points in Stable Subjects (n=38)	35%	6%

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Table 7

Gender as proxy for Exposure

Females Subjects in Stable Subgroup			Females Subjects in Experienced Site Group		
Response Definition	BHV-4157 (n=18)	Placebo (n=15)	Response Definition	BHV-4157 (n=17)	Placebo (n=18)
≥ 3 points	39%	0	≥ 3 points	41%	6%
≥ 1 point	67%	33%	≥ 1 point	71%	28%

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Table 16

8 WEEK CHANGE FROM BASELINE

			Enriched Genotypes	
	Total SARA	Mod SARA	Stable 2	Stable 1
Value – BHV3157	-0.91	-0.429	-0.387	-0.286
Value – Placebo	-1.103	-0.382	-0.148	-0.083

STABLE 1 = 1 unit change between Baseline & Screening total SARA
STABLE 2 = 2 unit change between baseline and screening total SARA

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Table 1

STABLE Subjects, defined by SCR-to-BL SARA within 1 point#

Stable baseline defined as Total SARA scores at screening and baseline within the group median of 1 point, comprising 63 subjects (49% of total sample)

	BHV-4157	Placebo	Δ Btw Groups [95% CI]	Response Definition	BHV-4157	Placebo	*p-value
Total SARA STABLE	-0.90 (n=34)	-0.50 (n=29)	-0.39 [-1.2 – 0.45]	≥ 3 points	24%	3.4%	0.03
Total SARA UNSTABLE	-0.87 (n=28)	-1.49 (n=38)	0.62 [-0.61 – 1.85]	≥ 1 point	59%	41%	0.21

*, *fisher exact test without correction for multiple comparisons*

	STABLE		NOT- STABLE	
	BHV-4157 (n=34)	Placebo (n=29)	BHV-4157 (n=28)	Placebo (n=38)
Total SARA	-0.90	-0.50	-0.87	-1.49
Axial SARA [#1 – 4]	-0.27	0.18	-0.46	-0.48
Appendicular SARA [4-8]	-0.36	-0.44	-0.15	-0.69

#, *≤ 1 point on Total SARA score 1*

Table 2

Population selected based on Experience of Site/Raters

Sites selected on the basis that the Principal Investigator has over two decades of ataxia research and PIs are raters, represents 72 subjects (55% of total sample)

	BHV-4157 (n=37)	**Placebo (n=35)**	**Δ Btw Groups [95% CI]**
Total SARA	-1.37	-0.97	-0.40 [-1.3 – 0.52]
Gait [#1]	-0.14	-0.06	-0.08 [-0.29 – 0.14]
Axial Items [#1 – 4]	-0.47	0.05	-0.52 [-1.1 – 0.07]
Appendicular [#5 – 8]	-0.52	-0.68	0.16 [-0.39 – 0.72]

**, analytic model identical to primary, presenting LSmeans*

Response Definition	**BHV-4157**	**Placebo**	***p-value**
≥ 3 points	21.6%	5.7%	0.09
≥ 1 point	51.4%	31.4%	0.10

**, fisher exact test without correction for multiple comparisons*

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Table 3

Population selected based on Experience of Site/Raters

	BHV-4157 (n=37)	Placebo (n=35)	Δ Btw Groups [95% CI]
Total SARA	-1.37	-0.97	-0.40 [-1.3 – 0.52]
Gait [#1]	-0.14	-0.06	-0.08 [-0.29 – 0.14]
Axial Items [#1 – 4]	-0.47	0.05	-0.52 [-1.1 – 0.07]
Appendicular [#5 – 8]	-0.52	-0.68	0.16 [-0.39 – 0.72]

**, analytic model identical to primary, presenting LSmeans*

- **Assuming true difference from data above, 500 subjects per arm would be required to provide 90% power for a randomized controlled trial**
  - ➢ A study this large is prohibitive for orphan indication and presents challenges in detecting signals at 8-weeks
  - ➢ Placebo effects may extinguish over long-term
  - ➢ Longitudinal cohort can be compared to Natural History Cohort to demonstrate neuroprotective effects

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Table 4

Exposure Proxy: Weight (lighter)

- Sample divided by median weight (≤76.4 kg vs >76.4 kg)
- Lighter median had crude preliminary estimate of 40% greater exposure (using unmodeled data) and Phase 1 studies show correlation of weight with exposure

Lighter median	BHV-4157 (n=27)	Placebo (n=39)	Δ Btw Groups [95% CI]
Total SARA*	-1.38	-0.89	-0.50 [-1.6 – 0.60]
Axial Items [1 – 4]	-0.85	-0.49	
Appendicular Items [5 - 8]	-0.69	-0.46	

	Change in Total SARA Score			Responder Analysis			
Efficacy Sample	BHV-4157	Placebo	Δ SARA [95% CI]	Response Definition	BHV-4157	Placebo	P-value*
All Lighter Subjects	-1.38 (n=27)	-0.89 (n=39)	-0.50 [-1.6 – 0.60]	≥ 3 points in All Subjects (n=65)	33%	18%	0.24
STABLE Subgroup	-1.18 (n=19)	-0.35 (n=17)	-0.83	≥ 3 points at Experienced sites (n=36)	26%	0	0.05
EXP Sites	-1.64 (n=18)	-0.61 (n=19)	-1.03	≥ 3 points in Stable Subjects (n=36)	39%	5%	0.02

**, fisher exact test without correction for multiple comparisons*

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Table 5

Exposure Proxy: Weight

- Examination of PGIC and CGI – no correlation or trend in general population or general subpopulations
- Trends in lighter weight sample (from total subset and among experienced sites)

CGI	Sample	BHV-4157	Placebo
Any Improvement	Lighter	64% (n=22)	45% (n=29)
Much Improved	"	27%	7%
Any Improvement	Lighter at EXP sites	60% (n=15)	33% (n=12)
Much Improved	"	14%	3%

PGI	Sample	BHV-4157	Placebo
Any Improvement	Lighter	34% (n=23)	20% (n=29)
"Better and Definite improvement that has made a real & worthwhile difference"	"	17%	0
Any Improvement	Lighter at EXP sites	45% (n=16)	8% (n=12)
Better and Definite...	"	19%	0

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Table 6

Gender as proxy for Exposure

- Females have greater may have approximately 50% greater exposure based on Phase 1 data (c/w Rilutek USPI)

	Change in Total SARA Score		Responder Analysis		
Females	BHV-4157	Placebo	Response Definition	BHV-4157	Placebo
All Subjects	-1.08 (n=31)	-0.83 (n=36)	≥ 3 points in All Subjects (n=67)	32%	17%
STABLE Subgroup	-1.33 (n=18)	-0.40 (n=15)	≥ 3 points at Experienced sites (n=33)	39%	0
Experience of Sites	-1.15 (n=20)	-0.64 (n=18)	≥ 3 points in Stable Subjects (n=38)	35%	6%

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Table 7

Gender as proxy for Exposure

Females Subjects in Stable Subgroup			Females Subjects in Experienced Site Group		
Response Definition	**BHV-4157 (n=18)**	**Placebo (n=15)**	**Response Definition**	**BHV-4157 (n=17)**	**Placebo (n=18)**
≥ 3 points	39%	0	≥ 3 points	41%	6%
≥ 1 point	67%	33%	≥ 1 point	71%	28%

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Table 16

8 WEEK CHANGE FROM BASELINE

			Enriched Genotypes	
	Total SARA.	Mod SARA.	Stable 2	Stable 1
Value – BHV5157	-0.81	-0.429	-0.387	-0.286
Value – Placebo	-1.103	-0.382	-0.148	-0.083

STABLE 1 = I unit change between Baseline & Screening total SARA
STABLE 2 = 2 unit change between baseline and screening total SARA

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