Dossier zur Nutzenbewertung gemäß § 35a SGB V

Olipudase alfa (Xenpozyme®)

Sanofi-Aventis Deutschland GmbH

Modul 4 A – Anhang 4-G

Manifestationen eines Mangels an saurer Sphingomyelinase (Acid Sphingomyelinase Deficiency, ASMD)

Ergänzende Analysen

Stand: 04.05.2026

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1 Studie ASCEND - Datenschnitt vom 15.03.2021

1.1 Splenomegaly-related score (SRS)

1.1.1 Analysis of the change in splenomegaly-related score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6 Efficacy response data

16.2.6.3 Splenomegaly-related Score

16.2.6.3.1 Analysis of the change in splenomegaly-related score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Baseline	Number of patients with value	17	18	
	Mean (SD)	28.051 (10.5594)	24.552 (11.1307)	
	Median	24.860	20.800	
	Min : Max	10.17 : 48.00	9.00 : 47.67	
Week 14	Number of patients with value	15	16	
	LS Mean	-6.278	-5.334	0.944
	SE	1.9386	1.8805	2.7235
	95% CI [1]	(-10.226,-2.330)	(-9.165,-1.502)	(-4.603,6.492)
	P-value for the within treatment comparison [1]	0.0028	0.0079	
	P-value for the difference between groups [1]			0.7311
	Mean (SD)	-7.027 (7.9827)	-5.219 (7.4076)	

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
[1] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline SAF1-Splenomegaly Related Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
[2] The p-value is based on a Wilcoxon-Mann-Whitney test and the missing data at Week 52 were imputed using LOCF by considering the last available post-baseline data.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Note: Baseline value for each patient was calculated from the data collected at the randomization visit (Week 0/Day 1). When patients answered all eDiary questions 0 at the randomization visit, the baseline value was calculated from the data collected at the screening.
Current data cutoff: 15MAR2021
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Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6 Efficacy response data

16.2.6.3 Splenomegaly-related Score

16.2.6.3.1 Analysis of the change in splenomegaly-related score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Week 26	Number of patients with value	15	17	
	LS Mean	-7.733	-5.949	1.783
	SE	1.9645	1.8959	2.7511
	95% CI [1]	(-11.739,-3.726)	(-9.819,-2.079)	(-3.829,7.396)
	P-value for the within treatment comparison [1]	0.0004	0.0038	
	P-value for the difference between groups [1]			0.5217
	Mean (SD)	-7.071 (8.6606)	-6.055 (7.1407)	
Week 38	Number of patients with value	17	17	
	LS Mean	-8.651	-7.549	1.102
	SE	2.2225	2.1650	3.1216

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
[1] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline SAF1-Splenomegaly Related Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
[2] The p-value is based on a Wilcoxon-Mann-Whitney test and the missing data at Week 52 were imputed using LOCF by considering the last available post-baseline data.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Note: Baseline value for each patient was calculated from the data collected at the randomization visit (Week 0/Day 1). When patients answered all eDiary questions 0 at the randomization visit, the baseline value was calculated from the data collected at the screening.
Current data cutoff: 15MAR2021
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Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6 Efficacy response data

16.2.6.3 Splenomegaly-related Score

16.2.6.3.1 Analysis of the change in splenomegaly-related score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
	95% CI [1]	(-13.197,-4.106)	(-11.975,-3.122)	(-5.279,7.484)
	P-value for the within treatment comparison [1]	0.0005	0.0016	
	P-value for the difference between groups [1]			0.7265
	Mean (SD)	-8.763 (8.9378)	-7.711 (9.3404)	
Week 52	Number of patients with value	15	16	
	LS Mean	-9.281	-7.664	1.618
	SE	2.4165	2.3481	3.3877
	95% CI [1]	(-14.219,-4.344)	(-12.461,-2.866)	(-5.302,8.538)
	P-value for the within treatment comparison [1]	0.0006	0.0028	
	P-value for the difference between groups [1]			0.6364
	Mean (SD)	-9.809 (10.3882)	-7.009 (9.0688)	

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
[1] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline SAF1-Splenomegaly Related Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
[2] The p-value is based on a Wilcoxon-Mann-Whitney test and the missing data at Week 52 were imputed using LOCF by considering the last available post-baseline data.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Note: Baseline value for each patient was calculated from the data collected at the randomization visit (Week 0/Day 1). When patients answered all eDiary questions 0 at the randomization visit, the baseline value was calculated from the data collected at the screening.
Current data cutoff: 15MAR2021
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Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6 Efficacy response data

16.2.6.3 Splenomegaly-related Score

16.2.6.3.1 Analysis of the change in splenomegaly-related score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

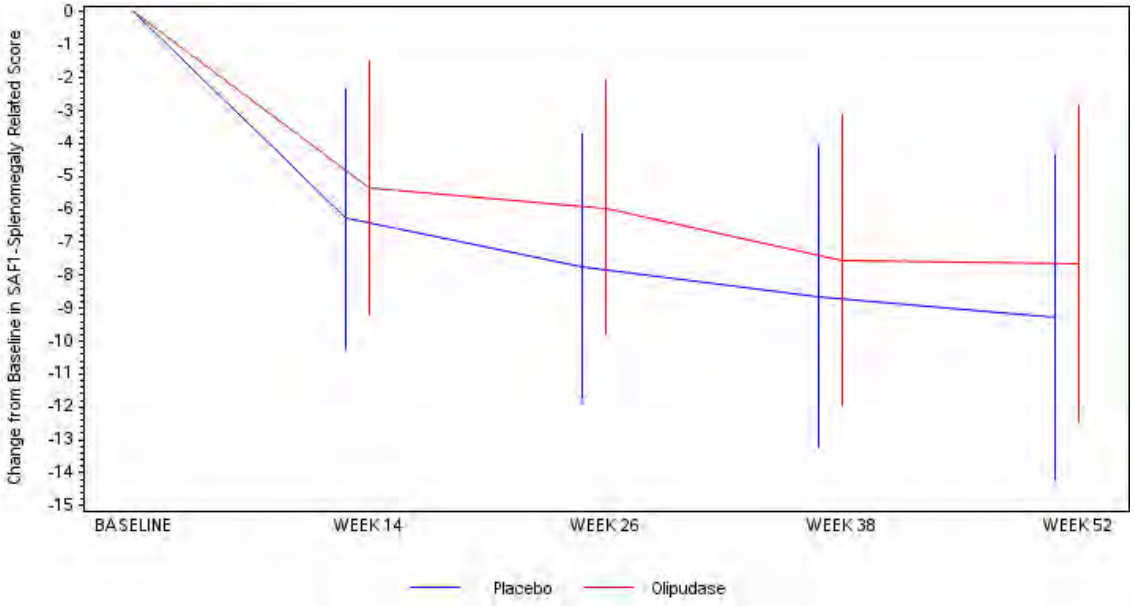
Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
	P-value for the difference between groups [2]			0.6440

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
[1] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline SAF1-Splenomegaly Related Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
[2] The p-value is based on a Wilcoxon-Mann-Whitney test and the missing data at Week 52 were imputed using LOCF by considering the last available post-baseline data.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Note: Baseline value for each patient was calculated from the data collected at the randomization visit (Week 0/Day 1). When patients answered all eDiary questions 0 at the randomization visit, the baseline value was calculated from the data collected at the screening.
Current data cutoff: 15MAR2021
PGM=PRODOPS/GZ402665/DFI12712/CSR_02/REPORT/PGM/mmrm_t.sas OUT=REPORT/OUTPUT/qs_mmrm_i_t_srsmean_x.rtf (11JUN2021 - 12:13)

1.1.2 Summary plot of the LS means from the MMRM of the change in splenomegaly-related score from baseline to 52 weeks in PAP - mITT population

Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6	Efficacy response data
16.2.6.3	Splenomegaly-related Score
16.2.6.3.2	Summary plot of the LS means from the MMRM of the change in splenomegaly-related score from baseline to 52 weeks in PAP - mITT population



Note: The vertical bars represent the 95% CIs for the LS means.
Note: The LSmeans and 95% CIs are based on a mixed model for repeated measures approach with baseline SAF1-Splenomegaly Related Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.
Note: * indicates nominal p-value <0.05, ** indicates nominal p-value <0.01, *** indicates nominal p-value <0.001.
Current data cutoff: 15MAR2021
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1.2 BFI – Item 3

1.2.1 Analysis of the change in BFI – Item 3 from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population

1.8 Analysis of the change in Brief Fatigue Inventory (BFI) Fatigue at its worst last 24 hours from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1.8.1 Overall

1.8.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	18	18
	Mean (SD)	5.056 (2.2874)	4.778 (3.0785)
	Median	5.000	6.000
	Min : Max	0.00 : 9.00	0.00 : 9.00
Week 26	Absolute change from baseline		
	Number of patients with value	17	15
	Mean (SD)	-0.765 (2.6108)	-1.133 (2.8502)
	LS Mean (SE)	-0.760 (0.5593)	-1.220 (0.5909)
	95% CI[a]	(-1.903,0.382)	(-2.426,-0.014)
	P-value for the within treatment comparison[a]	0.1842	0.0476
	LS Mean Diff (SE) vs. Placebo + BSC	0.460 (0.8151)	-
	95% CI	(-1.205,2.124)	-
	P-value for the difference between groups[a]	0.5770	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.195 (-0.511,0.901)	-
Week 52	Absolute change from baseline		
	Number of patients with value	18	17

Note: Only data until week 52 were taken into account

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.

Note: The variance-covariance structure used in the MMRM is Unstructured covariance.

[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.

Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population

1.8 Analysis of the change in Brief Fatigue Inventory (BFI) Fatigue at its worst last 24 hours from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1.8.1 Overall

1.8.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	-1.000 (3.0486)	-1.000 (3.6401)
	LS Mean (SE)	-1.052 (0.6721)	-0.981 (0.6916)
	95% CI[a]	(-2.422,0.318)	(-2.391,0.429)
	P-value for the within treatment comparison[a]	0.1276	0.1659
	LS Mean Diff (SE) vs. Placebo + BSC	-0.071 (0.9651)	-
	95% CI	(-2.038,1.896)	-
	P-value for the difference between groups[a]	0.9419	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.024 (-0.698,0.649)	-

Note: Only data until week 52 were taken into account

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.

Note: The variance-covariance structure used in the MMRM is Unstructured covariance.

[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.

Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

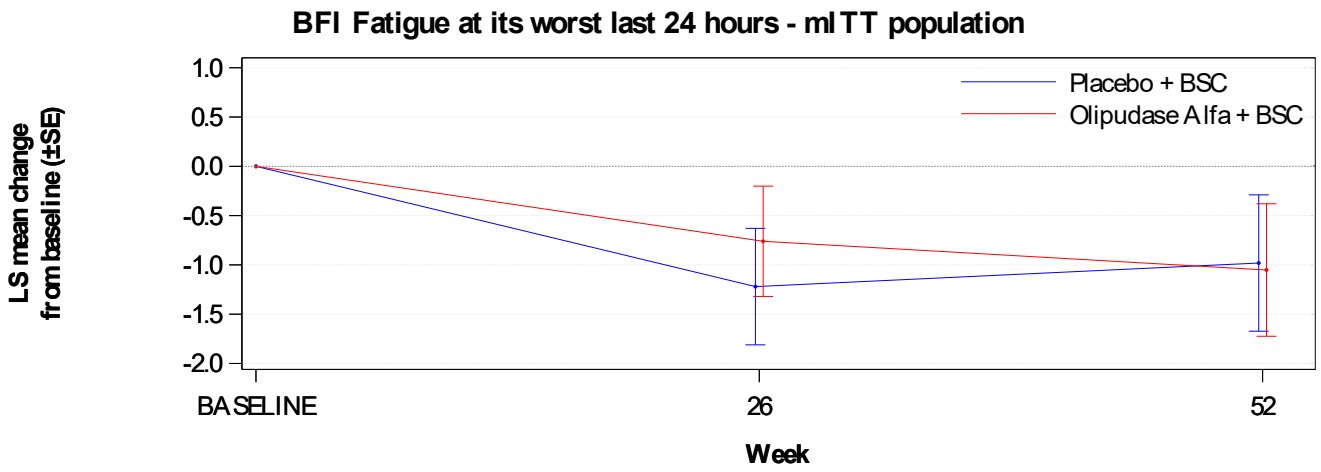
1.2.2 Summary plot of the LS means from the MMRM of the change in BFI – Item 3 from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population

1.8 Analysis of the change in Brief Fatigue Inventory (BFI) Fatigue at its worst last 24 hours from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1.8.1 Overall

1.8.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	18	15	17
Olipudase Alfa + BSC	18	17	18

Note: Only data until week 52 were taken into account

Note: The vertical bars represent standard errors.

Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

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1.3 BPI – Item 3

1.3.1 Analysis of the change in BPI – Item 3 from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population

1.19 Analysis of the change in Brief Pain Inventory - Short Form (BPI-SF) Pain on the average from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1.19.1 Overall

1.19.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	15	12
	Mean (SD)	4.800 (1.7403)	5.667 (2.1462)
	Median	5.000	6.000
	Min : Max	2.00 : 8.00	2.00 : 9.00
Week 26	Absolute change from baseline		
	Number of patients with value	11	9
	Mean (SD)	-1.091 (2.1192)	-2.889 (2.3688)
	LS Mean (SE)	-1.466 (0.5572)	-2.298 (0.6116)
	95% CI[a]	(-2.653,-0.279)	(-3.599,-0.997)
	P-value for the within treatment comparison[a]	0.0188	0.0018
	LS Mean Diff (SE) vs. Placebo + BSC	0.832 (0.8290)	-
	95% CI	(-0.932,2.596)	-
	P-value for the difference between groups[a]	0.3313	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.429 (-0.481,1.339)	-
Week 52	Absolute change from baseline		
	Number of patients with value	12	8

Note: Only data until week 52 were taken into account

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.

Note: The variance-covariance structure used in the MMRM is Unstructured covariance.

[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.

Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population

1.19 Analysis of the change in Brief Pain Inventory - Short Form (BPI-SF) Pain on the average from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1.19.1 Overall

1.19.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	-1.833 (2.2896)	-1.875 (3.7961)
	LS Mean (SE)	-1.961 (0.6952)	-1.503 (0.8021)
	95% CI[a]	(-3.422,-0.500)	(-3.177,0.171)
	P-value for the within treatment comparison[a]	0.0114	0.0757
	LS Mean Diff (SE) vs. Placebo + BSC	-0.458 (1.0619)	-
	95% CI	(-2.679,1.764)	-
	P-value for the difference between groups[a]	0.6713	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.187 (-1.092,0.719)	-

Note: Only data until week 52 were taken into account

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.

Note: The variance-covariance structure used in the MMRM is Unstructured covariance.

[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.

Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

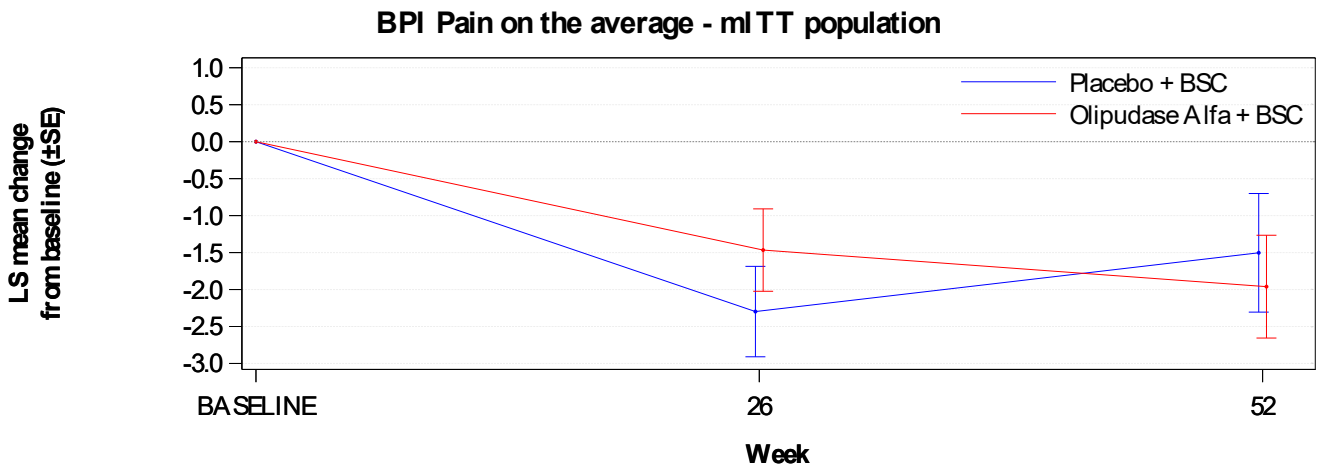
1.3.2 Summary plot of the LS means from the MMRM of the change in BPI – Item 3 from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population

1.19 Analysis of the change in Brief Pain Inventory - Short Form (BPI-SF) Pain on the average from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1.19.1 Overall

1.19.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	12	9	8
Olipudase Alfa + BSC	15	11	12

Note: Only data until week 52 were taken into account

Note: The vertical bars represent standard errors.

Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

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1.4 FACIT – Dyspnea symptom scale score

1.4.1 Analysis of the change in FACIT – Dyspnea symptom scale score from baseline to 52 weeks using a mixed model for repeated measures in PAP -mITT Population

Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6 Efficacy response data

16.2.6.8 FACIT-Dyspnea Symptom score

16.2.6.8.1 Analysis of the change in FACIT-Dyspnea symptom scale score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT Population

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Baseline	Number of patients with value	14	17	
	Mean (SD)	49.714 (9.2236)	48.959 (9.1209)	
	Median	48.800	48.800	
	Min : Max	27.70 : 61.20	32.80 : 69.50	
Week 14	Number of patients with value	10	13	
	LS Mean	-3.247	-2.777	0.470
	SE	2.0751	1.8199	2.7618
	95% CI [1]	(-7.531,1.037)	(-6.532,0.978)	(-5.225,6.165)
	P-value for the within treatment comparison [1]	0.1308	0.1400	
	P-value for the difference between groups [1]			0.8663
	Mean (SD)	-2.830 (7.8320)	-2.046 (6.4605)	
Week 26	Number of patients with value	9	16	
	LS Mean	-5.711	-2.710	3.001

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
[1] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline FACIT1-Dyspnea Symptom Scale Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Current data cutoff: 15MAR2021
PGM=PRODOPS/GZ402665/DFI12712/CSR_02/REPORT/PGM/mmrm_t.sas OUT=REPORT/OUTPUT/qs_mmrm_i_t_facit1ds_x.rtf (11JUN2021 - 12:14)

Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6 Efficacy response data

16.2.6.8 FACIT-Dyspnea Symptom score

16.2.6.8.1 Analysis of the change in FACIT-Dyspnea symptom scale score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT Population

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
	SE	1.9577	1.5955	2.5280
	95% CI [1]	(-9.740,-1.681)	(-6.017,0.597)	(-2.213,8.215)
	P-value for the within treatment comparison [1]	0.0073	0.1034	
	P-value for the difference between groups [1]			0.2466
	Mean (SD)	-4.444 (6.1250)	-2.331 (6.9979)	
Week 38	Number of patients with value	11	15	
	LS Mean	-5.677	-3.921	1.755
	SE	1.8019	1.5720	2.3907
	95% CI [1]	(-9.388,-1.966)	(-7.161,-0.682)	(-3.169,6.680)
	P-value for the within treatment comparison [1]	0.0042	0.0197	
	P-value for the difference between groups [1]			0.4696
	Mean (SD)	-5.736 (7.0570)	-3.533 (6.6265)	
Week 52	Number of patients with value	11	14	

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
[1] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline FACIT1-Dyspnea Symptom Scale Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Current data cutoff: 15MAR2021
PGM=PRODOPS/GZ402665/DFI12712/CSR_02/REPORT/PGM/mmrm_t.sas OUT=REPORT/OUTPUT/qs_mmrm_i_t_facit1ds_x.rtf (11JUN2021 - 12:14)

Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6 Efficacy response data

16.2.6.8 FACIT-Dyspnea Symptom score

16.2.6.8.1 Analysis of the change in FACIT-Dyspnea symptom scale score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT Population

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
	LS Mean	-6.769	-5.862	0.907
	SE	1.9132	1.6918	2.5536
	95% CI [1]	(-10.708,-2.831)	(-9.344,-2.380)	(-4.349,6.162)
	P-value for the within treatment comparison [1]	0.0016	0.0019	
	P-value for the difference between groups [1]			0.7255
	Mean (SD)	-6.964 (8.6093)	-7.021 (5.2545)	

SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
[1] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline FACIT1-Dyspnea Symptom Scale Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Current data cutoff: 15MAR2021
PGM=PRODOPS/GZ402665/DFI12712/CSR_02/REPORT/PGM/mmrm_t.sas OUT=REPORT/OUTPUT/qs_mmrm_i_t_facit1ds_x.rtf (11JUN2021 - 12:14)

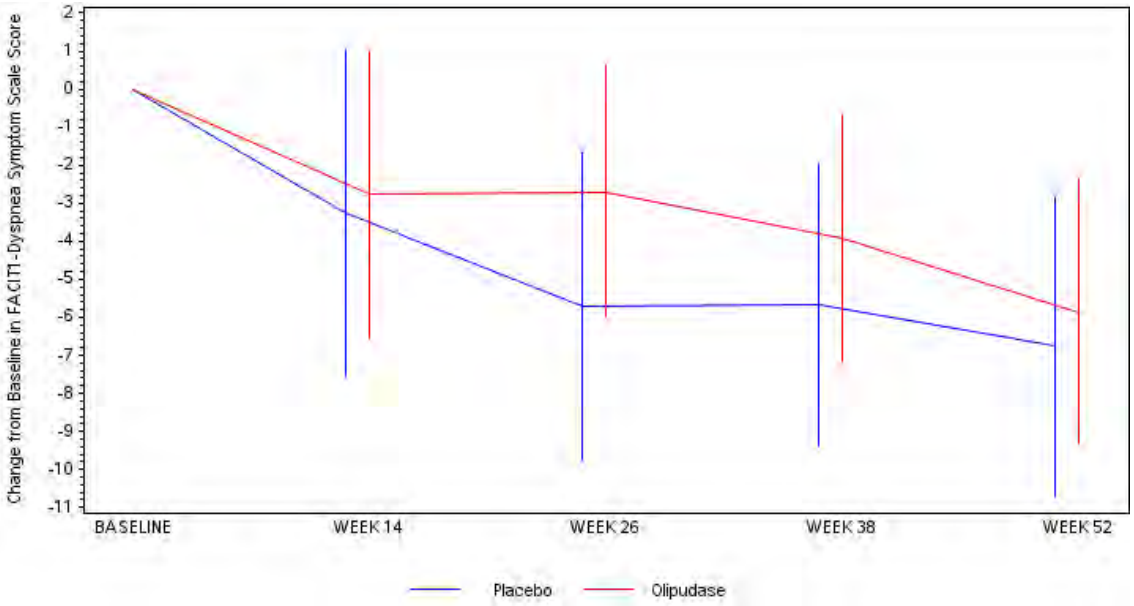
1.4.2 Plot of LS means from the MMRM of the change in FACIT – Dyspnea symptom scale score from baseline to 52 weeks in PAP - mITT population

Project Code / Study Number / Analysis: GZ402665 / DFI12712 / CSR_02

16.2.6 Efficacy response data

16.2.6.8 FACIT-Dyspnea Symptom score

16.2.6.8.2 Summary plot of the LS means from the MMRM of the change in FACIT-Dyspnea symptom scale score from baseline to 52 weeks in PAP - mITT population



Note: The vertical bars represent the 95% CIs for the LS means.

Note: The LSmeans and 95% CIs are based on a mixed model for repeated measures approach with baseline FACIT1-Dyspnea Symptom Scale Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

Note: * indicates nominal p-value <0.05, ** indicates nominal p-value <0.01, *** indicates nominal p-value <0.001.

Current data cutoff: 15MAR2021

PGM=PRODOPS/GZ402665/DFI12712/CSR_02/REPORT/PGM/mmrm_g.sas OUT=REPORT/OUTPUT/mmrm_g_facit1ds_x.rtf (11JUN2021 - 12:15)

1.5 PGIS

1.5.1 Analysis of the change in PGIS-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.28 Analysis of the change in PGIS-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.28.1 Overall
1.28.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	12	14
	Mean (SD)	1.917 (1.2401)	1.929 (1.1411)
	Median	2.000	2.000
	Min : Max	0.00 : 4.00	0.00 : 4.00
Week 14	Absolute change from baseline		
	Number of patients with value	10	11
	Mean (SD)	-0.500 (1.0801)	-0.273 (0.9045)
	LS Mean (SE)	-0.504 (0.2336)	-0.183 (0.2232)
	95% CI[a]	(-0.997,-0.012)	(-0.653,0.287)
	P-value for the within treatment comparison[a]	0.0451	0.4228
	LS Mean Diff (SE) vs. Placebo + BSC	-0.321 (0.3237)	-
	95% CI	(-1.003,0.360)	-
	P-value for the difference between groups[a]	0.3345	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.415 (-1.297,0.466)	-
Week 26	Absolute change from baseline		
	Number of patients with value	11	11

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
PGM=DEVOPS/GZ402665/DFI12712/CSR_03_HEVA/REPORT/PGM/eff_mmrm_ger_i_t.sas OUT=REPORT/OUTPUT/eff_mmrm_pgi01_chg_ger_i_t_x.rtf (20APR2026 15:52)

1 Continuous endpoints - mITT population
1.28 Analysis of the change in PGIS-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.28.1 Overall
1.28.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	-0.636 (1.0269)	-0.545 (1.0357)
	LS Mean (SE)	-0.743 (0.2463)	-0.562 (0.2450)
	95% CI[a]	(-1.266,-0.221)	(-1.080,-0.044)
	P-value for the within treatment comparison[a]	0.0082	0.0353
	LS Mean Diff (SE) vs. Placebo + BSC	-0.182 (0.3475)	-
	95% CI	(-0.917,0.554)	-
	P-value for the difference between groups[a]	0.6080	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.213 (-1.073,0.648)	-
Week 38	Absolute change from baseline		
	Number of patients with value	10	12
	Mean (SD)	-0.200 (1.3166)	-0.750 (1.3568)
	LS Mean (SE)	-0.239 (0.3156)	-0.719 (0.2854)
	95% CI[a]	(-0.899,0.420)	(-1.316,-0.122)
	P-value for the within treatment comparison[a]	0.4570	0.0208
	LS Mean Diff (SE) vs. Placebo + BSC	0.480 (0.4259)	-
	95% CI	(-0.410,1.370)	-
	P-value for the difference between groups[a]	0.2737	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.464 (-0.397,1.326)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population
1.28 Analysis of the change in PGIS-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.28.1 Overall
1.28.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 52	Absolute change from baseline		
	Number of patients with value	12	13
	Mean (SD)	-0.667 (1.0731)	-0.462 (1.0500)
	LS Mean (SE)	-0.754 (0.2427)	-0.505 (0.2326)
	95% CI[a]	(-1.258,-0.251)	(-0.988,-0.023)
	P-value for the within treatment comparison[a]	0.0051	0.0410
	LS Mean Diff (SE) vs. Placebo + BSC	-0.249 (0.3356)	-
	95% CI	(-0.946,0.447)	-
	P-value for the difference between groups[a]	0.4655	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.287 (-1.087,0.514)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
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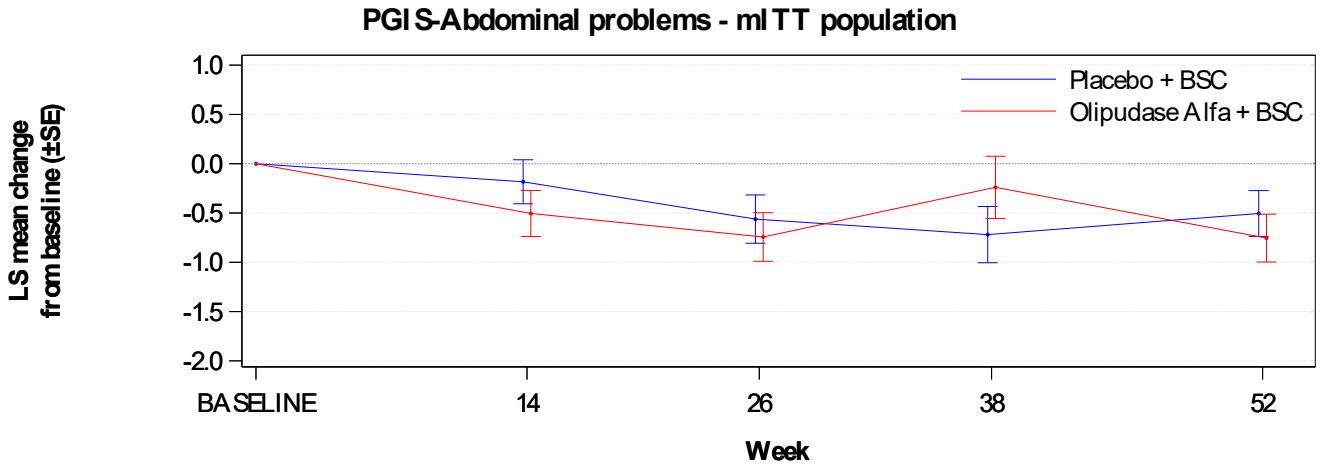
1.5.2 Summary plot of the LS means from the MMRM of the change in PGIS-Abdominal problems from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.28 Analysis of the change in PGIS-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.28.1 Overall
1.28.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	14	11	11	12	13
Olipudase Alfa + BSC	12	10	11	10	12

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.5.3 Analysis of the change in PGIS-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.29 Analysis of the change in PGIS-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.29.1 Overall
1.29.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	12	14
	Mean (SD)	1.500 (1.0871)	1.643 (1.2157)
	Median	1.000	2.000
	Min : Max	0.00 : 3.00	0.00 : 4.00
Week 14	Absolute change from baseline		
	Number of patients with value	10	11
	Mean (SD)	-1.000 (0.9428)	-0.818 (1.5374)
	LS Mean (SE)	-1.024 (0.2677)	-0.722 (0.2558)
	95% CI[a]	(-1.580,-0.468)	(-1.253,-0.190)
	P-value for the within treatment comparison[a]	0.0010	0.0101
	LS Mean Diff (SE) vs. Placebo + BSC	-0.302 (0.3710)	-
	95% CI	(-1.073,0.468)	-
	P-value for the difference between groups[a]	0.4238	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.344 (-1.221,0.532)	-
Week 26	Absolute change from baseline		
	Number of patients with value	11	11

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
PGM=DEVOPS/GZ402665/DFI12712/CSR_03_HEVA/REPORT/PGM/eff_mmrm_ger_i_t.sas OUT=REPORT/OUTPUT/eff_mmrm_pgi02_chg_ger_i_t_x.rtf (20APR2026 15:52)

1 Continuous endpoints - mITT population
1.29 Analysis of the change in PGIS-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.29.1 Overall
1.29.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	-0.273 (1.0090)	-0.636 (1.5667)
	LS Mean (SE)	-0.385 (0.2828)	-0.679 (0.2752)
	95% CI[a]	(-0.976,0.207)	(-1.253,-0.104)
	P-value for the within treatment comparison[a]	0.1897	0.0230
	LS Mean Diff (SE) vs. Placebo + BSC	0.294 (0.3949)	-
	95% CI	(-0.531,1.119)	-
	P-value for the difference between groups[a]	0.4653	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.305 (-0.551,1.162)	-
Week 38	Absolute change from baseline		
	Number of patients with value	10	12
	Mean (SD)	-0.200 (1.2293)	-0.333 (1.5570)
	LS Mean (SE)	-0.360 (0.3387)	-0.315 (0.3129)
	95% CI[a]	(-1.063,0.343)	(-0.966,0.337)
	P-value for the within treatment comparison[a]	0.3001	0.3261
	LS Mean Diff (SE) vs. Placebo + BSC	-0.045 (0.4612)	-
	95% CI	(-1.003,0.914)	-
	P-value for the difference between groups[a]	0.9235	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.040 (-0.897,0.817)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

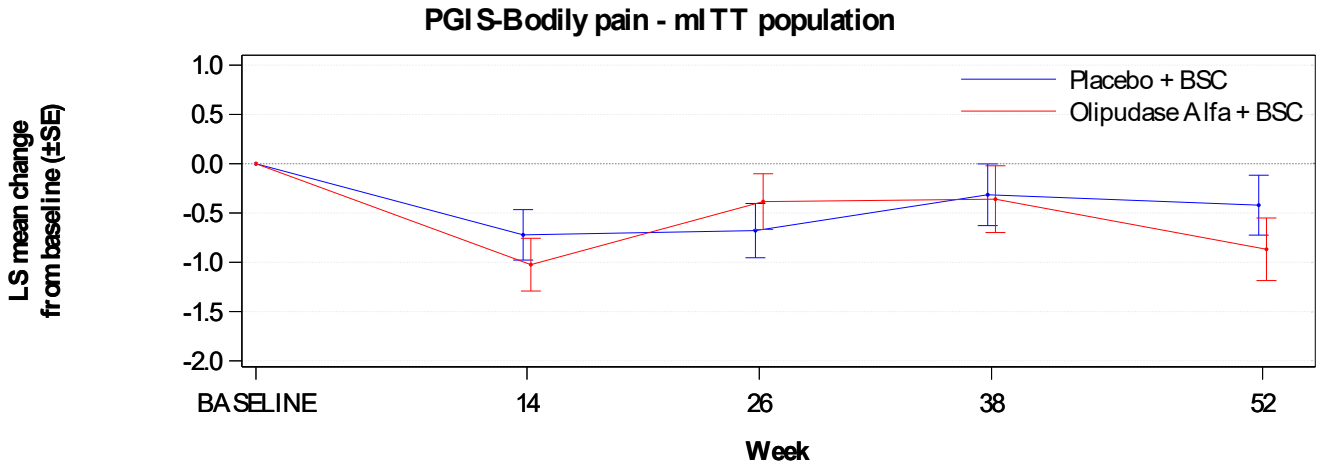
1 Continuous endpoints - mITT population
1.29 Analysis of the change in PGIS-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.29.1 Overall
1.29.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 52	Absolute change from baseline		
	Number of patients with value	12	13
	Mean (SD)	-0.750 (0.9653)	-0.385 (1.5566)
	LS Mean (SE)	-0.868 (0.3174)	-0.420 (0.3038)
	95% CI[a]	(-1.526,-0.210)	(-1.051,0.210)
	P-value for the within treatment comparison[a]	0.0121	0.1803
	LS Mean Diff (SE) vs. Placebo + BSC	-0.447 (0.4388)	-
	95% CI	(-1.357,0.462)	-
	P-value for the difference between groups[a]	0.3189	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.394 (-1.194,0.407)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
PGM=DEVOPS/GZ402665/DFI12712/CSR_03_HEVA/REPORT/PGM/eff_mmrm_ger_i_t.sas OUT=REPORT/OUTPUT/eff_mmrm_pgi02_chg_ger_i_t_x.rtf (20APR2026 15:52)

1.5.4 Summary plot of the LS means from the MMRM of the change in PGIS-Bodily pain from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.29 Analysis of the change in PGIS-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.29.1 Overall
1.29.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	14	11	11	12	13
Olipudase Alfa + BSC	12	10	11	10	12

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.5.5 Analysis of the change in PGIS-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.30 Analysis of the change in PGIS-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.30.1 Overall
1.30.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	12	14
	Mean (SD)	2.250 (0.9653)	2.286 (1.2044)
	Median	2.000	2.500
	Min : Max	0.00 : 4.00	0.00 : 4.00
Week 14	Absolute change from baseline		
	Number of patients with value	10	11
	Mean (SD)	-0.400 (0.9661)	-0.364 (0.9244)
	LS Mean (SE)	-0.473 (0.2628)	-0.278 (0.2505)
	95% CI[a]	(-1.024,0.077)	(-0.802,0.247)
	P-value for the within treatment comparison[a]	0.0878	0.2815
	LS Mean Diff (SE) vs. Placebo + BSC	-0.196 (0.3643)	-
	95% CI	(-0.958,0.566)	-
	P-value for the difference between groups[a]	0.5973	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.226 (-1.107,0.654)	-
Week 26	Absolute change from baseline		
	Number of patients with value	11	11

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population
1.30 Analysis of the change in PGIS-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.30.1 Overall
1.30.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	-0.364 (1.1201)	-0.545 (0.6876)
	LS Mean (SE)	-0.477 (0.2125)	-0.537 (0.2064)
	95% CI[a]	(-0.922,-0.032)	(-0.968,-0.106)
	P-value for the within treatment comparison[a]	0.0369	0.0173
	LS Mean Diff (SE) vs. Placebo + BSC	0.060 (0.2970)	-
	95% CI	(-0.561,0.681)	-
	P-value for the difference between groups[a]	0.8424	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.083 (-0.776,0.941)	-
Week 38	Absolute change from baseline		
	Number of patients with value	10	12
	Mean (SD)	-0.300 (1.0593)	-0.500 (0.6742)
	LS Mean (SE)	-0.338 (0.2513)	-0.480 (0.2326)
	95% CI[a]	(-0.862,0.185)	(-0.966,0.006)
	P-value for the within treatment comparison[a]	0.1927	0.0526
	LS Mean Diff (SE) vs. Placebo + BSC	0.142 (0.3431)	-
	95% CI	(-0.574,0.857)	-
	P-value for the difference between groups[a]	0.6843	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.170 (-0.690,1.030)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

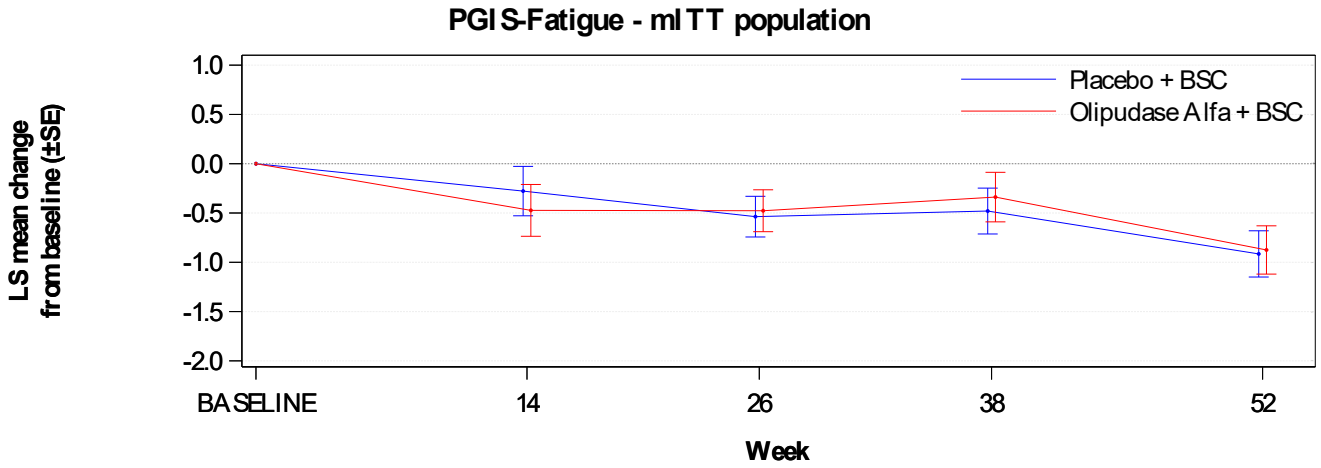
1 Continuous endpoints - mITT population
1.30 Analysis of the change in PGIS-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.30.1 Overall
1.30.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 52	Absolute change from baseline		
	Number of patients with value	12	13
	Mean (SD)	-0.833 (1.1146)	-0.923 (0.9541)
	LS Mean (SE)	-0.875 (0.2449)	-0.915 (0.2345)
	95% CI[a]	(-1.384,-0.365)	(-1.403,-0.427)
	P-value for the within treatment comparison[a]	0.0018	0.0008
	LS Mean Diff (SE) vs. Placebo + BSC	0.040 (0.3391)	-
	95% CI	(-0.666,0.746)	-
	P-value for the difference between groups[a]	0.9070	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.046 (-0.757,0.848)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
PGM=DEVOPS/GZ402665/DFI12712/CSR_03_HEVA/REPORT/PGM/eff_mmrm_ger_i_t.sas OUT=REPORT/OUTPUT/eff_mmrm_pgi03_chg_ger_i_t_x.rtf (20APR2026 15:52)

1.5.6 Summary plot of the LS means from the MMRM of the change in PGIS-Fatigue from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.30 Analysis of the change in PGIS-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.30.1 Overall
1.30.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	14	11	11	12	13
Olipudase Alfa + BSC	12	10	11	10	12

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.5.7 Analysis of the change in PGIS-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.31 Analysis of the change in PGIS-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.31.1 Overall
1.31.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	12	14
	Mean (SD)	1.750 (0.9653)	1.143 (1.0271)
	Median	2.000	1.000
	Min : Max	0.00 : 3.00	0.00 : 3.00
Week 14	Absolute change from baseline		
	Number of patients with value	10	11
	Mean (SD)	-0.400 (0.9661)	-0.182 (1.1677)
	LS Mean (SE)	-0.197 (0.2050)	-0.356 (0.1959)
	95% CI[a]	(-0.626,0.232)	(-0.765,0.054)
	P-value for the within treatment comparison[a]	0.3489	0.0849
	LS Mean Diff (SE) vs. Placebo + BSC	0.159 (0.2890)	-
	95% CI	(-0.446,0.764)	-
	P-value for the difference between groups[a]	0.5888	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.235 (-0.660,1.130)	-
Week 26	Absolute change from baseline		
	Number of patients with value	11	11

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population
1.31 Analysis of the change in PGIS-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.31.1 Overall
1.31.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	-0.182 (1.0787)	-0.182 (1.2505)
	LS Mean (SE)	0.011 (0.2757)	-0.306 (0.2665)
	95% CI[a]	(-0.564,0.586)	(-0.861,0.249)
	P-value for the within treatment comparison[a]	0.9694	0.2646
	LS Mean Diff (SE) vs. Placebo + BSC	0.316 (0.3887)	-
	95% CI	(-0.493,1.126)	-
	P-value for the difference between groups[a]	0.4250	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.339 (-0.528,1.206)	-
Week 38	Absolute change from baseline		
	Number of patients with value	10	12
	Mean (SD)	-0.300 (1.3375)	-0.167 (1.1934)
	LS Mean (SE)	-0.093 (0.3015)	-0.385 (0.2849)
	95% CI[a]	(-0.719,0.532)	(-0.977,0.208)
	P-value for the within treatment comparison[a]	0.7597	0.1912
	LS Mean Diff (SE) vs. Placebo + BSC	0.291 (0.4201)	-
	95% CI	(-0.581,1.163)	-
	P-value for the difference between groups[a]	0.4955	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.289 (-0.577,1.155)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

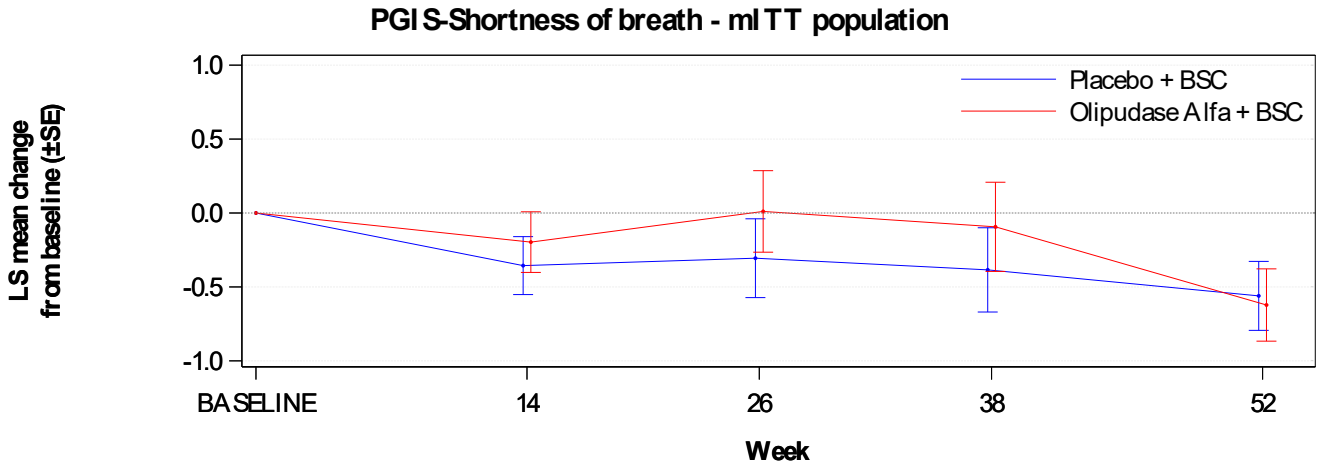
1 Continuous endpoints - mITT population
1.31 Analysis of the change in PGIS-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.31.1 Overall
1.31.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 52	Absolute change from baseline		
	Number of patients with value	12	13
	Mean (SD)	-0.917 (1.1645)	-0.308 (1.1821)
	LS Mean (SE)	-0.622 (0.2444)	-0.560 (0.2332)
	95% CI[a]	(-1.129,-0.116)	(-1.044,-0.077)
	P-value for the within treatment comparison[a]	0.0183	0.0251
	LS Mean Diff (SE) vs. Placebo + BSC	-0.062 (0.3456)	-
	95% CI	(-0.777,0.653)	-
	P-value for the difference between groups[a]	0.8596	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.071 (-0.890,0.749)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.5.8 Summary plot of the LS means from the MMRM of the change in PGIS-Shortness of breath from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.31 Analysis of the change in PGIS-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.31.1 Overall
1.31.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	14	11	11	12	13
Olipudase Alfa + BSC	12	10	11	10	12

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.6 PGIC

1.6.1 Analysis of the change in PGIC-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.32 Analysis of PGIC-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.32.1 Overall
1.32.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 14	Value		
	Number of patients with value	12	11
	Mean (SD)	0.833 (1.3371)	1.091 (1.0445)
	LS Mean (SE)	0.879 (0.3106)	1.149 (0.3256)
	95% CI[a]	(0.242,1.516)	(0.481,1.817)
	P-value for the within treatment comparison[a]	0.0086	0.0015
	LS Mean Diff (SE) vs. Placebo + BSC	-0.271 (0.4500)	-
	95% CI	(-1.193,0.652)	-
	P-value for the difference between groups[a]	0.5527	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.244 (-1.076,0.588)	-
Week 26	Value		
	Number of patients with value	13	11
	Mean (SD)	0.462 (1.2659)	0.455 (1.0357)
	LS Mean (SE)	0.522 (0.3215)	0.754 (0.3409)
	95% CI[a]	(-0.138,1.182)	(0.054,1.454)
	P-value for the within treatment comparison[a]	0.1165	0.0358
	LS Mean Diff (SE) vs. Placebo + BSC	-0.232 (0.4686)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population
1.32 Analysis of PGIC-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.32.1 Overall
1.32.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI	(-1.194,0.730)	-
	P-value for the difference between groups[a]	0.6244	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.197 (-1.012,0.619)	-
Week 38	Value		
	Number of patients with value	15	15
	Mean (SD)	0.933 (1.5796)	0.667 (1.1751)
	LS Mean (SE)	1.080 (0.3380)	0.621 (0.3491)
	95% CI[a]	(0.391,1.768)	(-0.092,1.334)
	P-value for the within treatment comparison[a]	0.0032	0.0855
	LS Mean Diff (SE) vs. Placebo + BSC	0.459 (0.4857)	-
	95% CI	(-0.532,1.449)	-
	P-value for the difference between groups[a]	0.3522	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.336 (-0.390,1.063)	-
Week 52	Value		
	Number of patients with value	18	16
	Mean (SD)	1.278 (1.2744)	0.563 (1.2093)
	LS Mean (SE)	1.275 (0.2983)	0.543 (0.3170)

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

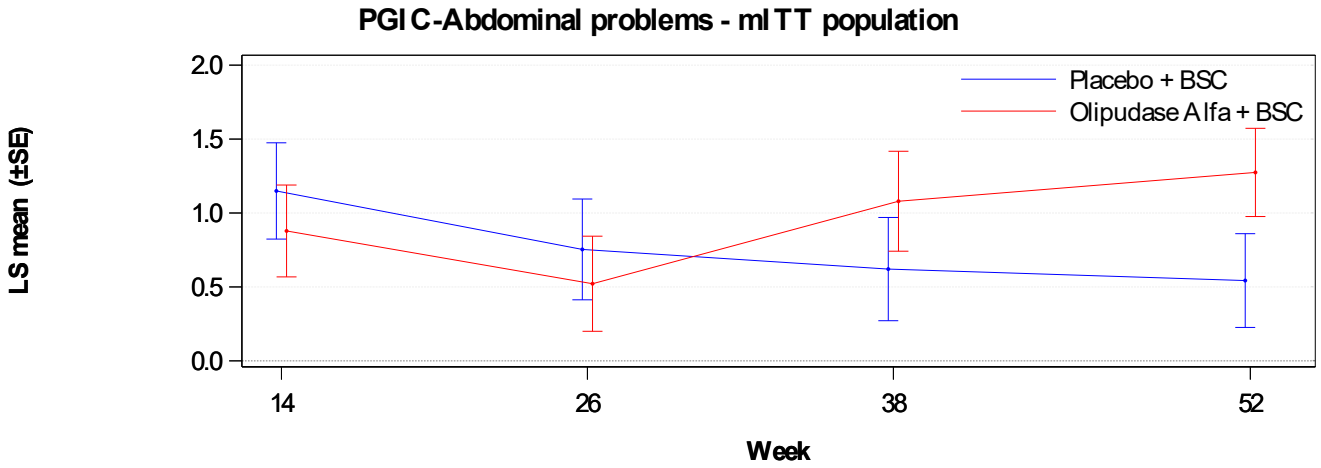
1 Continuous endpoints - mITT population
1.32 Analysis of PGIC-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.32.1 Overall
1.32.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI[a]	(0.666,1.883)	(-0.104,1.190)
	P-value for the within treatment comparison[a]	0.0002	0.0967
	LS Mean Diff (SE) vs. Placebo + BSC	0.731 (0.4351)	-
	95% CI	(-0.156,1.619)	-
	P-value for the difference between groups[a]	0.1029	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.563 (-0.120,1.247)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.6.2 Summary plot of the LS means from the MMRM of the change in PGIC-Abdominal problems from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.32 Analysis of PGIC-Abdominal problems from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.32.1 Overall
1.32.1.2 Plot of least squares means



Number of Patients

Placebo + BSC	11	11	15	16
Olipudase Alfa + BSC	12	13	15	18

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.6.3 Analysis of the change in PGIC-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.33 Analysis of PGIC-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.33.1 Overall
1.33.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 14	Value		
	Number of patients with value	12	11
	Mean (SD)	0.500 (1.0871)	0.818 (1.0787)
	LS Mean (SE)	0.539 (0.2969)	0.890 (0.3110)
	95% CI[a]	(-0.071,1.150)	(0.251,1.530)
	P-value for the within treatment comparison[a]	0.0809	0.0082
	LS Mean Diff (SE) vs. Placebo + BSC	-0.351 (0.4299)	-
	95% CI	(-1.235,0.533)	-
	P-value for the difference between groups[a]	0.4217	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.331 (-1.164,0.502)	-
Week 26	Value		
	Number of patients with value	13	11
	Mean (SD)	0.615 (1.1929)	0.545 (1.1282)
	LS Mean (SE)	0.693 (0.3156)	0.870 (0.3372)
	95% CI[a]	(0.045,1.341)	(0.178,1.562)
	P-value for the within treatment comparison[a]	0.0370	0.0156
	LS Mean Diff (SE) vs. Placebo + BSC	-0.177 (0.4619)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population
1.33 Analysis of PGIC-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.33.1 Overall
1.33.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI	(-1.125,0.771)	-
	P-value for the difference between groups[a]	0.7045	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.152 (-0.968,0.663)	-
Week 38	Value		
	Number of patients with value	15	15
	Mean (SD)	0.933 (1.2799)	0.467 (0.8338)
	LS Mean (SE)	0.964 (0.2681)	0.441 (0.2734)
	95% CI[a]	(0.418,1.511)	(-0.118,1.000)
	P-value for the within treatment comparison[a]	0.0011	0.1175
	LS Mean Diff (SE) vs. Placebo + BSC	0.523 (0.3827)	-
	95% CI	(-0.258,1.305)	-
	P-value for the difference between groups[a]	0.1815	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.487 (-0.240,1.213)	-
Week 52	Value		
	Number of patients with value	18	16
	Mean (SD)	1.056 (1.2590)	0.625 (1.2583)
	LS Mean (SE)	1.053 (0.2994)	0.612 (0.3179)

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

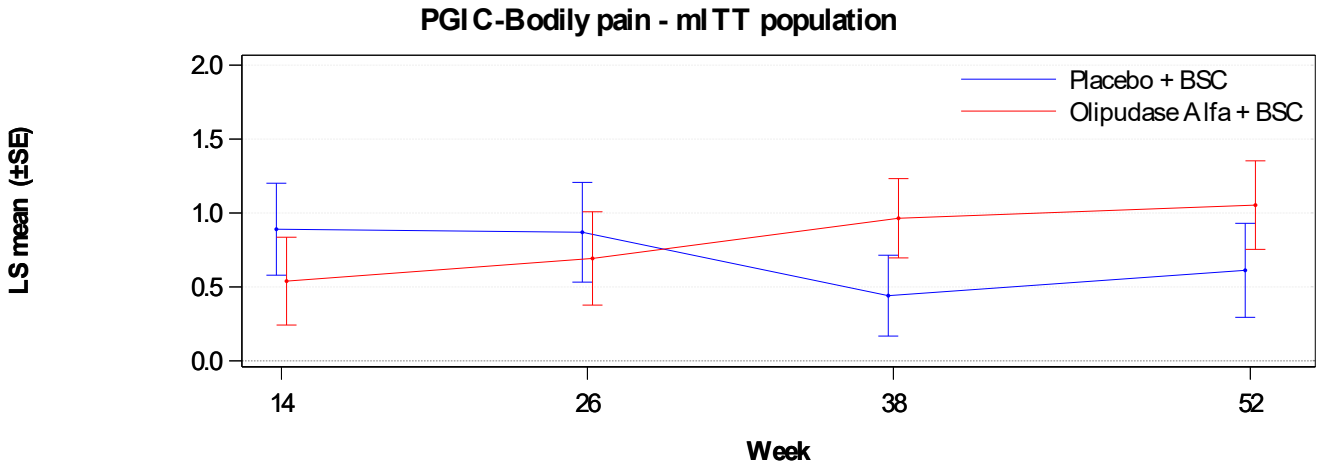
1 Continuous endpoints - mITT population
1.33 Analysis of PGIC-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.33.1 Overall
1.33.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI[a]	(0.443,1.664)	(-0.035,1.260)
	P-value for the within treatment comparison[a]	0.0013	0.0631
	LS Mean Diff (SE) vs. Placebo + BSC	0.441 (0.4366)	-
	95% CI	(-0.449,1.331)	-
	P-value for the difference between groups[a]	0.3201	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.339 (-0.345,1.022)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.6.4 Summary plot of the LS means from the MMRM of the change in PGIC-Bodily pain from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.33 Analysis of PGIC-Bodily pain from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.33.1 Overall
1.33.1.2 Plot of least squares means



Number of Patients

Placebo + BSC	11	11	15	16
Olipudase Alfa + BSC	12	13	15	18

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.6.5 Analysis of the change in PGIC-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.34 Analysis of PGIC-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.34.1 Overall
1.34.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 14	Value		
	Number of patients with value	12	11
	Mean (SD)	1.000 (0.9535)	0.182 (1.3280)
	LS Mean (SE)	1.032 (0.3277)	0.194 (0.3431)
	95% CI[a]	(0.355,1.709)	(-0.516,0.903)
	P-value for the within treatment comparison[a]	0.0044	0.5782
	LS Mean Diff (SE) vs. Placebo + BSC	0.838 (0.4746)	-
	95% CI	(-0.143,1.819)	-
	P-value for the difference between groups[a]	0.0904	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.714 (-0.121,1.549)	-
Week 26	Value		
	Number of patients with value	13	11
	Mean (SD)	0.692 (0.9473)	0.000 (0.4472)
	LS Mean (SE)	0.771 (0.2181)	0.133 (0.2336)
	95% CI[a]	(0.321,1.221)	(-0.348,0.615)
	P-value for the within treatment comparison[a]	0.0017	0.5734
	LS Mean Diff (SE) vs. Placebo + BSC	0.638 (0.3196)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population
1.34 Analysis of PGIC-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.34.1 Overall
1.34.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI	(-0.021,1.297)	-
	P-value for the difference between groups[a]	0.0573	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.791 (-0.026,1.609)	-
Week 38	Value		
	Number of patients with value	15	15
	Mean (SD)	0.867 (1.0601)	0.067 (1.6676)
	LS Mean (SE)	0.828 (0.3535)	0.047 (0.3600)
	95% CI[a]	(0.107,1.550)	(-0.690,0.783)
	P-value for the within treatment comparison[a]	0.0258	0.8974
	LS Mean Diff (SE) vs. Placebo + BSC	0.781 (0.5043)	-
	95% CI	(-0.249,1.812)	-
	P-value for the difference between groups[a]	0.1319	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.551 (-0.176,1.278)	-
Week 52	Value		
	Number of patients with value	18	16
	Mean (SD)	1.111 (1.3235)	0.438 (1.0935)
	LS Mean (SE)	1.111 (0.2895)	0.437 (0.3073)

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

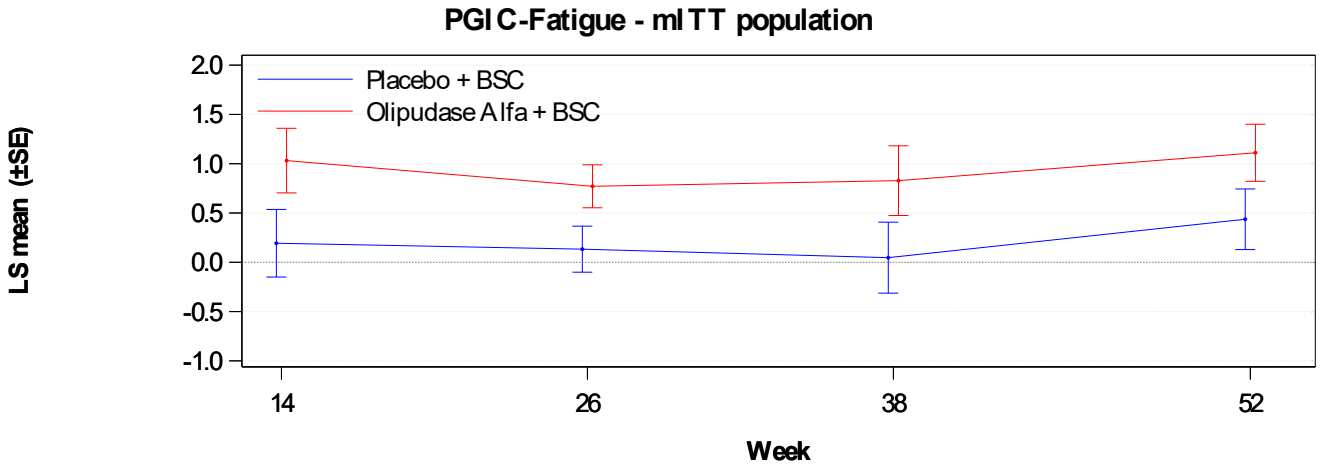
1 Continuous endpoints - mITT population
1.34 Analysis of PGIC-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.34.1 Overall
1.34.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI[a]	(0.521,1.701)	(-0.190,1.063)
	P-value for the within treatment comparison[a]	0.0006	0.1651
	LS Mean Diff (SE) vs. Placebo + BSC	0.674 (0.4221)	-
	95% CI	(-0.186,1.534)	-
	P-value for the difference between groups[a]	0.1200	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.536 (-0.147,1.219)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.6.6 Summary plot of the LS means from the MMRM of the change in PGIC-Fatigue from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.34 Analysis of PGIC-Fatigue from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.34.1 Overall
1.34.1.2 Plot of least squares means



Number of Patients

Placebo + BSC	11	11	15	16
Olipudase Alfa + BSC	12	13	15	18

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.6.7 Analysis of the change in PGIC-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.35 Analysis of PGIC-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.35.1 Overall
1.35.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 14	Value		
	Number of patients with value	11	11
	Mean (SD)	0.727 (1.1037)	0.455 (0.9342)
	LS Mean (SE)	0.843 (0.2691)	0.460 (0.2746)
	95% CI[a]	(0.293,1.394)	(-0.103,1.022)
	P-value for the within treatment comparison[a]	0.0040	0.1052
	LS Mean Diff (SE) vs. Placebo + BSC	0.384 (0.3846)	-
	95% CI	(-0.403,1.171)	-
	P-value for the difference between groups[a]	0.3268	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.414 (-0.436,1.264)	-
Week 26	Value		
	Number of patients with value	13	10
	Mean (SD)	0.769 (1.1658)	0.400 (1.0750)
	LS Mean (SE)	0.920 (0.3111)	0.634 (0.3447)
	95% CI[a]	(0.278,1.562)	(-0.076,1.343)
	P-value for the within treatment comparison[a]	0.0069	0.0777
	LS Mean Diff (SE) vs. Placebo + BSC	0.286 (0.4643)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population
1.35 Analysis of PGIC-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.35.1 Overall
1.35.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI	(-0.671,1.243)	-
	P-value for the difference between groups[a]	0.5439	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.250 (-0.587,1.087)	-
Week 38	Value		
	Number of patients with value	15	15
	Mean (SD)	1.067 (1.0998)	0.133 (1.3558)
	LS Mean (SE)	1.081 (0.3117)	0.109 (0.3167)
	95% CI[a]	(0.445,1.717)	(-0.539,0.756)
	P-value for the within treatment comparison[a]	0.0016	0.7335
	LS Mean Diff (SE) vs. Placebo + BSC	0.972 (0.4441)	-
	95% CI	(0.065,1.879)	-
	P-value for the difference between groups[a]	0.0365	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.779 (0.052,1.505)	-
Week 52	Value		
	Number of patients with value	17	16
	Mean (SD)	1.176 (1.1311)	0.313 (1.0782)
	LS Mean (SE)	1.112 (0.2711)	0.299 (0.2853)

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

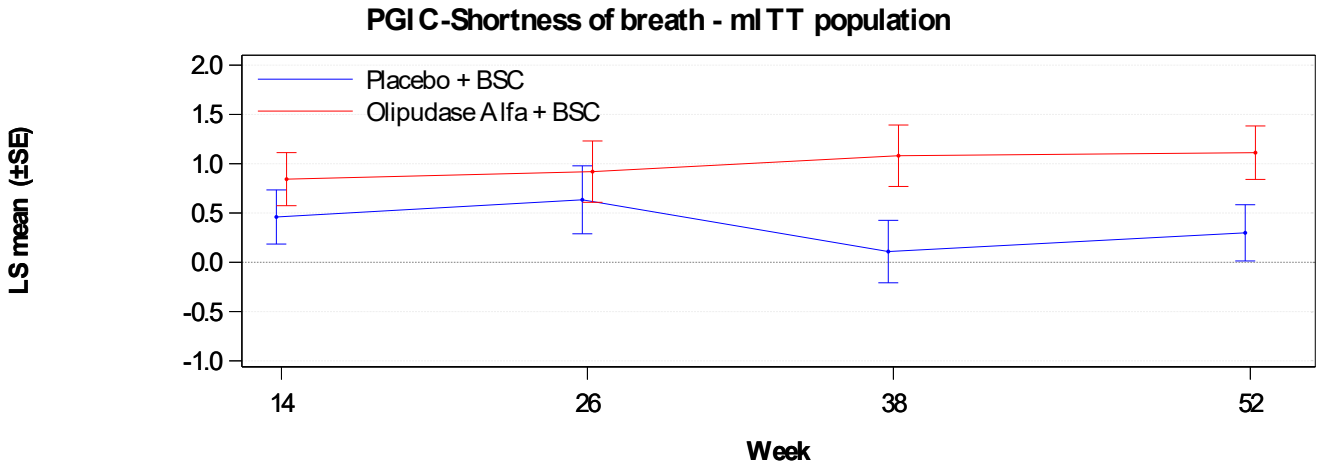
1 Continuous endpoints - mITT population
1.35 Analysis of PGIC-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.35.1 Overall
1.35.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI[a]	(0.559,1.665)	(-0.284,0.882)
	P-value for the within treatment comparison[a]	0.0003	0.3034
	LS Mean Diff (SE) vs. Placebo + BSC	0.813 (0.3935)	-
	95% CI	(0.010,1.617)	-
	P-value for the difference between groups[a]	0.0475	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.702 (0.008,1.396)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.6.8 Summary plot of the LS means from the MMRM of the change in PGIC-Shortness of breath from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.35 Analysis of PGIC-Shortness of breath from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.35.1 Overall
1.35.1.2 Plot of least squares means



Number of Patients

Placebo + BSC	11	10	15	16
Olipudase Alfa + BSC	11	13	15	17

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.6.9 Analysis of the change in PGIC-Ability to perform daily activities from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.36 Analysis of PGIC-Ability to perform daily activities from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.36.1 Overall
1.36.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Week 14	Value		
	Number of patients with value	11	11
	Mean (SD)	1.000 (1.0954)	0.636 (1.0269)
	LS Mean (SE)	1.026 (0.3079)	0.698 (0.3104)
	95% CI[a]	(0.390,1.662)	(0.056,1.339)
	P-value for the within treatment comparison[a]	0.0028	0.0343
	LS Mean Diff (SE) vs. Placebo + BSC	0.328 (0.4372)	-
	95% CI	(-0.575,1.231)	-
	P-value for the difference between groups[a]	0.4601	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.310 (-0.543,1.162)	-
Week 26	Value		
	Number of patients with value	13	10
	Mean (SD)	0.462 (0.6602)	0.100 (0.3162)
	LS Mean (SE)	0.499 (0.1538)	0.167 (0.1745)
	95% CI[a]	(0.179,0.819)	(-0.195,0.529)
	P-value for the within treatment comparison[a]	0.0038	0.3484
	LS Mean Diff (SE) vs. Placebo + BSC	0.332 (0.2327)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1 Continuous endpoints - mITT population
1.36 Analysis of PGIC-Ability to perform daily activities from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.36.1 Overall
1.36.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI	(-0.151,0.815)	-
	P-value for the difference between groups[a]	0.1679	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.579 (-0.263,1.421)	-
Week 38	Value		
	Number of patients with value	15	15
	Mean (SD)	0.867 (1.0601)	0.600 (0.8281)
	LS Mean (SE)	0.896 (0.2376)	0.580 (0.2419)
	95% CI[a]	(0.411,1.380)	(0.086,1.075)
	P-value for the within treatment comparison[a]	0.0007	0.0230
	LS Mean Diff (SE) vs. Placebo + BSC	0.315 (0.3390)	-
	95% CI	(-0.377,1.007)	-
	P-value for the difference between groups[a]	0.3598	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.331 (-0.396,1.058)	-
Week 52	Value		
	Number of patients with value	17	16
	Mean (SD)	1.412 (1.1757)	0.563 (1.1529)
	LS Mean (SE)	1.348 (0.2815)	0.564 (0.2945)

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

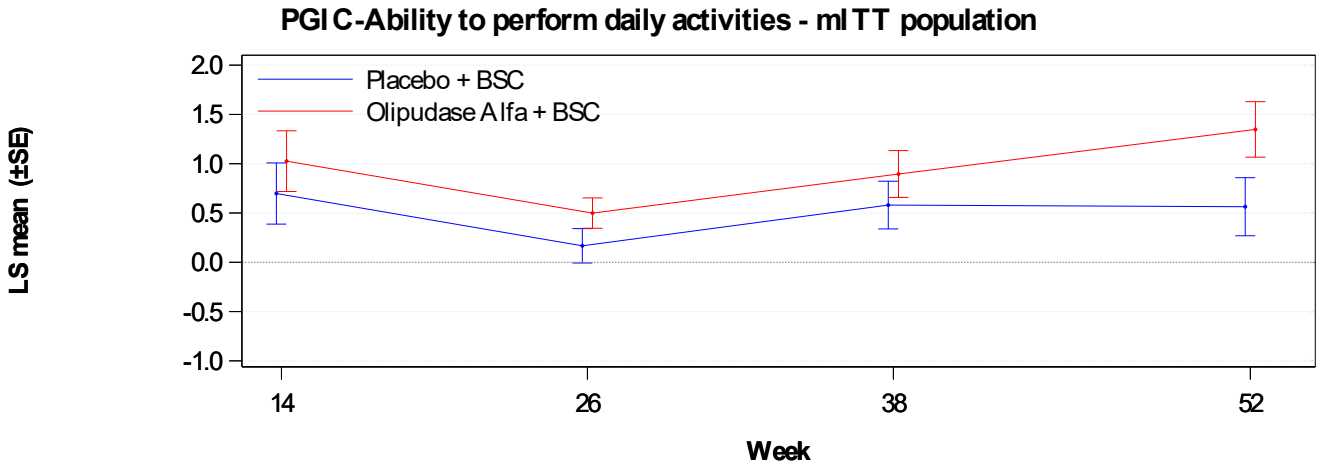
1 Continuous endpoints - mITT population
1.36 Analysis of PGIC-Ability to perform daily activities from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.36.1 Overall
1.36.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	95% CI[a]	(0.774,1.922)	(-0.037,1.165)
	P-value for the within treatment comparison[a]	<.0001	0.0649
	LS Mean Diff (SE) vs. Placebo + BSC	0.784 (0.4074)	-
	95% CI	(-0.047,1.615)	-
	P-value for the difference between groups[a]	0.0635	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.654 (-0.039,1.348)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.6.10 Summary plot of the LS means from the MMRM of the change in PGIC-Ability to perform daily activities from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.36 Analysis of PGIC-Ability to perform daily activities from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.36.1 Overall
1.36.1.2 Plot of least squares means



Number of Patients

Placebo + BSC	11	10	15	16
Olipudase Alfa + BSC	11	13	15	17

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.7 EQ-5D VAS

1.7.1 Analysis of the change in EQ-5D VAS from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.39 Analysis of the change in EQ VAS score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.39.1 Overall
1.39.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	18	18
	Mean (SD)	52.111 (16.9840)	63.889 (20.6907)
	Median	47.500	70.000
	Min : Max	25.00 : 80.00	30.00 : 95.00
Week 26	Absolute change from baseline		
	Number of patients with value	18	15
	Mean (SD)	17.889 (17.2077)	7.000 (25.8982)
	LS Mean (SE)	12.065 (3.8341)	15.648 (4.1152)
	95% CI[a]	(4.225,19.906)	(7.260,24.037)
	P-value for the within treatment comparison[a]	0.0038	0.0006
	LS Mean Diff (SE) vs. Placebo + BSC	-3.583 (5.7851)	-
	95% CI	(-15.383,8.217)	-
	P-value for the difference between groups[a]	0.5402	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.217 (-0.931,0.497)	-
Week 52	Absolute change from baseline		
	Number of patients with value	18	17

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
PGM=DEVOPS/GZ402665/DFI12712/CSR_03_HEVA/REPORT/PGM/eff_mmrm_ger_i_t.sas OUT=REPORT/OUTPUT/eff_mmrm_eqvas_chg_ger_i_t_x.rtf (20APR2026 15:52)

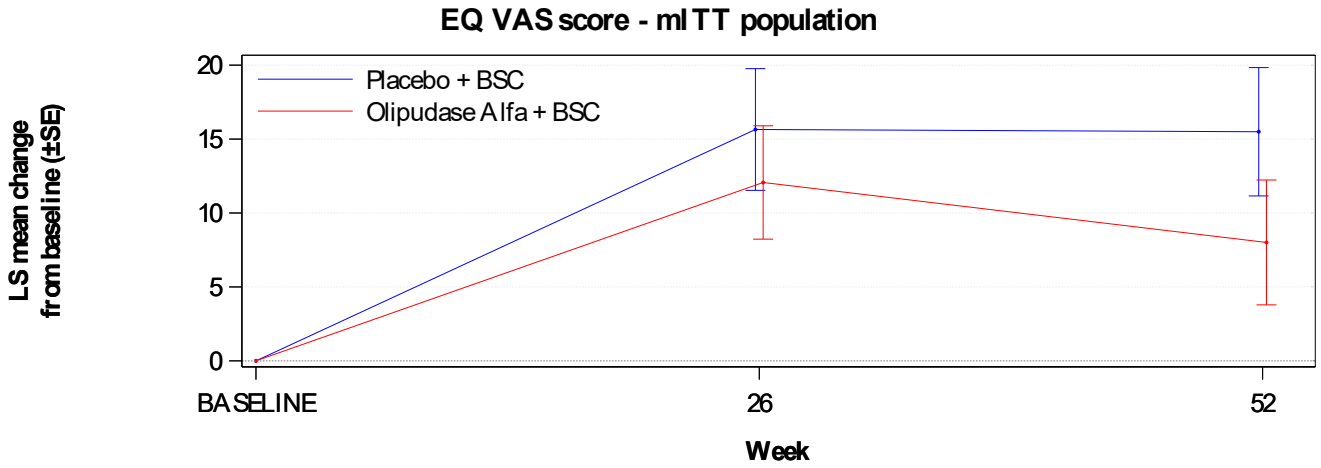
1 Continuous endpoints - mITT population
1.39 Analysis of the change in EQ VAS score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.39.1 Overall
1.39.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	13.833 (22.6696)	9.647 (29.3959)
	LS Mean (SE)	8.010 (4.2221)	15.495 (4.3394)
	95% CI[a]	(-0.594,16.614)	(6.651,24.339)
	P-value for the within treatment comparison[a]	0.0670	0.0012
	LS Mean Diff (SE) vs. Placebo + BSC	-7.485 (6.1883)	-
	95% CI	(-20.088,5.117)	-
	P-value for the difference between groups[a]	0.2353	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.408 (-1.096,0.279)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.7.2 Summary plot of the LS means from the MMRM of the change in EQ-5D VAS from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.39 Analysis of the change in EQ VAS score from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.39.1 Overall
1.39.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	18	15	17
Olipudase Alfa + BSC	18	18	18

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.8 SF-36

1.8.1 Analysis of the change in SF-36 Mental Component Summary from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.37 Analysis of the change in SF-36 Mental Component Summary from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.37.1 Overall
1.37.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	18	18
	Mean (SD)	43.782 (9.7113)	45.316 (10.2063)
	Median	45.600	45.460
	Min : Max	20.96 : 56.70	21.35 : 62.21
Week 26	Absolute change from baseline		
	Number of patients with value	18	15
	Mean (SD)	2.721 (10.2471)	1.543 (10.8377)
	LS Mean (SE)	2.806 (2.0281)	1.965 (2.1219)
	95% CI[a]	(-1.334,6.945)	(-2.358,6.289)
	P-value for the within treatment comparison[a]	0.1766	0.3613
	LS Mean Diff (SE) vs. Placebo + BSC	0.840 (2.9468)	-
	95% CI	(-5.169,6.850)	-
	P-value for the difference between groups[a]	0.7774	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.097 (-0.598,0.793)	-
Week 52	Absolute change from baseline		
	Number of patients with value	18	17

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

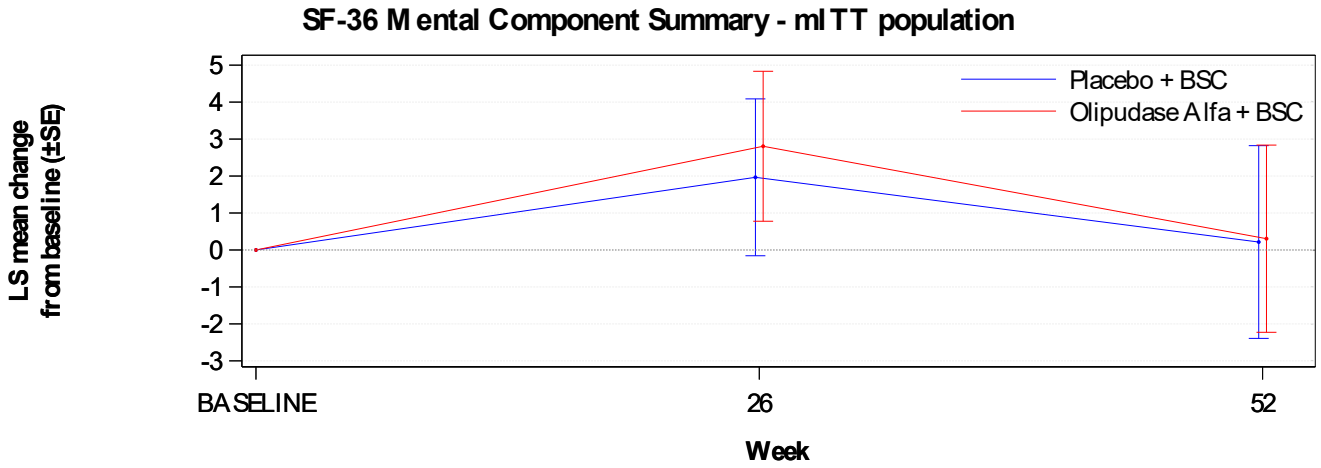
1 Continuous endpoints - mITT population
1.37 Analysis of the change in SF-36 Mental Component Summary from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.37.1 Overall
1.37.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	0.220 (11.8052)	0.214 (12.4714)
	LS Mean (SE)	0.305 (2.5324)	0.215 (2.6072)
	95% CI[a]	(-4.866,5.476)	(-5.109,5.539)
	P-value for the within treatment comparison[a]	0.9049	0.9348
	LS Mean Diff (SE) vs. Placebo + BSC	0.090 (3.6440)	-
	95% CI	(-7.350,7.530)	-
	P-value for the difference between groups[a]	0.9804	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.008 (-0.667,0.683)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.8.2 Summary plot of the LS means from the MMRM of the change in SF-36 Mental Component Summary from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.37 Analysis of the change in SF-36 Mental Component Summary from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.37.1 Overall
1.37.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	18	15	17
Olipudase Alfa + BSC	18	18	18

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

1.8.3 Analysis of the change in SF-36 Physical Component Summary from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population

1 Continuous endpoints - mITT population
1.38 Analysis of the change in SF-36 Physical Component Summary from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.38.1 Overall
1.38.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
Baseline	Number of patients with value	18	18
	Mean (SD)	37.623 (6.9720)	40.019 (10.7060)
	Median	39.495	39.335
	Min : Max	25.17 : 46.67	21.72 : 58.09
Week 26	Absolute change from baseline		
	Number of patients with value	18	15
	Mean (SD)	4.648 (8.4814)	8.444 (7.7751)
	LS Mean (SE)	4.178 (1.7925)	10.096 (1.8889)
	95% CI[a]	(0.511,7.846)	(6.241,13.951)
	P-value for the within treatment comparison[a]	0.0270	<.0001
	LS Mean Diff (SE) vs. Placebo + BSC	-5.918 (2.6143)	-
	95% CI	(-11.259,-0.577)	-
	P-value for the difference between groups[a]	0.0311	-
	Hedges'g vs. Placebo + BSC (95% CI)	-0.772 (-1.468,-0.075)	-
Week 52	Absolute change from baseline		
	Number of patients with value	18	17

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

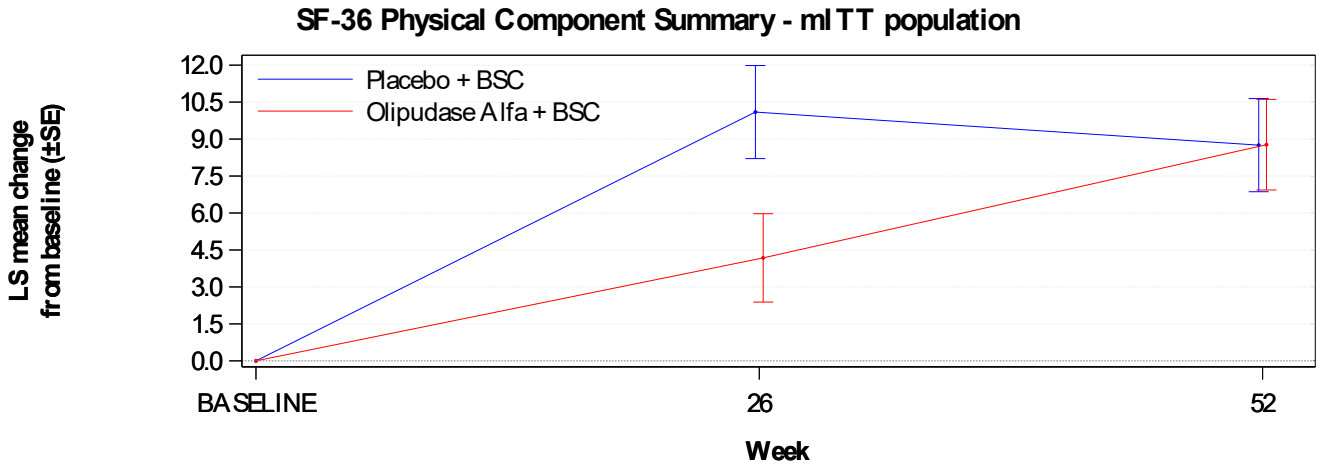
1 Continuous endpoints - mITT population
1.38 Analysis of the change in SF-36 Physical Component Summary from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.38.1 Overall
1.38.1.1 Table

Visit	Statistic	Olipudase alfa + BSC (N=18)	Placebo + BSC (N=18)
	Mean (SD)	9.242 (8.4397)	8.280 (9.8599)
	LS Mean (SE)	8.772 (1.8380)	8.754 (1.8907)
	95% CI[a]	(5.023,12.522)	(4.897,12.610)
	P-value for the within treatment comparison[a]	<.0001	<.0001
	LS Mean Diff (SE) vs. Placebo + BSC	0.019 (2.6463)	-
	95% CI	(-5.379,5.416)	-
	P-value for the difference between groups[a]	0.9945	-
	Hedges'g vs. Placebo + BSC (95% CI)	0.002 (-0.673,0.678)	-

Note: Only data until week 52 were taken into account
SD = Standard deviation; SE = Standard error; CI = Confidence interval; LS = Least squares.
Note: The variance-covariance structure used in the MMRM is Unstructured covariance.
[a] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

1.8.4 Summary plot of the LS means from the MMRM of the change in SF-36 Physical Component Summary from baseline to 52 weeks in PAP - mITT population

1 Continuous endpoints - mITT population
1.38 Analysis of the change in SF-36 Physical Component Summary from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population
1.38.1 Overall
1.38.1.2 Plot of least squares means of change from baseline



Number of Patients

Placebo + BSC	18	15	17
Olipudase Alfa + BSC	18	18	18

Note: Only data until week 52 were taken into account
Note: The vertical bars represent standard errors.
Note: The LSmeans and SE are based on a mixed model for repeated measures approach with baseline value for the endpoint being assessed, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.