Baseline Characteristics Across Major Clinical Trials in Progressive Multiple Sclerosis: Insights from ORATORIO, EXPAND, MS-STAT2, HERCULES, and CALLIPER.

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Background

Progressive multiple sclerosis (MS) involves the steady accumulation of neurological disability, with limited treatment options at this time. Several major trials have explored therapies in this domain, including ORATORIO (ocrelizumab, in primary progressive MS, PPMS), EXPAND (siponimod, in secondary progressive MS, SPMS), MS-STAT2 (simvastatin, in SPMS), and HERCULES (tolebrutinib, in non-relapsing SPMS, nrSPMS).

CALLIPER, a randomized, placebo-controlled phase 2 trial, explores vidofludimus calcium, a Nurr1 activator[1] and selective DHODH inhibitor[2], for its potential neuroprotective effects in SPMS and PPMS.

Objectives

To compare the baseline characteristics of patients in the CALLIPER subpopulations with major progressive MS (PMS) trials and discuss how differences may affect impact comparability of trial outcomes.

Methods

For this analysis, we extracted baseline characteristics, including age, disease duration, sex, Expanded Disability Status Scale (EDSS) scores, magnetic resonance imaging (MRI) findings as well as definitions of subpopulations, from the trials.

Results

CALLIPER consists of 278 patients with non-active SPMS[3] (59.5%, defined as no relapses within 24 months and no gadolinium-enhancing [Gd+] lesions within 12 months), 37 with active SPMS (7.9%, defined as no relapses within 24 months but with Gd+ lesions within 12 months) and 152 with PPMS (35.2%). CALLIPER is still blinded, and only pooled baseline characteristics for both treatment arms are available at this point.

The studies defined the respective SPMS populations differently, e.g., CALLIPER and HERCULES required no evidence of relapses in the 24 months before randomization; EXPAND 3 months). Nonetheless, the analysis revealed similarities in patient characteristics regarding age, sex, and EDSS.

Some differences were found regarding remaining focal inflammation, best exemplified by the presence of Gd+ lesions at baseline. 17.8% of the CALLIPER PPMS patients had Gd+ lesions (ORATORIO trial for PPMS, 26.5%). In the non-active SPMS CALLIPER population, 6.8% of patients had Gd+ lesions at baseline (HERCULES trial in nrSPMS patients 12.6%). In the small active SPMS group of CALLIPER, 64.4% of patients reported Gd+ lesions (EXPAND 45.7% on siponimod and 43.3% on placebo).

Conclusions

The data from CALLIPER will provide valuable insights into the effects of vidofludimus calcium in a non-active PMS population.

Any impact of vidofludimus calcium on 24-week confirmed disability worsening in this group would likely primarily reflect its influence on compartmentalized pathology within the CNS (expressed clinically as PIRA). Top-line CALLIPER data is expected in April 2025.

	Ocrelizumab	Placebo	Fingolimod	Placebo	Vidofludimus Calcium or Placebo (still blinded)	Siponimod	Placebo	Simvastatin	Placebo	Natalizumab	Placebo	Vidofludimus Calcium or Placebo (still blinded)	Tolebrutinib	Placebo	Vidofludimus Calcium or Placebo (still blinded)
	ORATORIO		INFORM		CALLIPER	EXPAND		MS-STAT2		ASCEND		CALLIPER	HERCULES 3		CALLIPER
	(N= 488)	(N= 244)	(N= 336)	(N= 487)	(N= 152)	(N=1105)	(N=546)	(N= 482)	(N= 482)	(N= 439)	(N= 448)	(N= 315)	(N= 754)	(N= 377)	(N= 267)[4]
Age (years)															
Mean	44.7 ±7.9	44.4 ±8.3	48.5 (8.6)	49.0 (27-65)	47.4 (11.308)	48.0 (7.8)	48.1 (7.9)	54 (7)	54 (7)	47.3 (7.4)	47.2 (7.8)	50.8 (8.5)	48.9 (8.0)	48.9 (8.0)	51.1 (8.7)
Median	46.0 (20-56)	46.0 (18-56)	49.0 (24-65)	49.0 (27-65)	48.0 (21-65)	49.0 (22.61)	49.0 (21.61)	–	–				–	–	51.0 (28-65)
Age group															
18-40 years	–	–	66 (19.7%)	94 (19.3%)	43 (28.3%)	188 (17%)	103 (19%)	–	–	–	–	37 (11.2%)			34 (12.7%)
>41 years	–	–	270 (80.3%)	393 (80.7%)	109 (72.0%)	917 (83%)	443 (81%)	–	–	–	–	278 (88.2%)			233 (87.2%)
Female sex-no. (%)	237 (48.6)	124 (50.8)	163 (48.5)	235 (48.3)	93 (61.1)	669 (61)	323 (59)	463 (96)	466 (97)	270 (62)	280 (63)	209 (66.3)	454 (60.2)	242 (64.2)	177 (66.3)
BMI															
Mean	24.8 (4.92)	25.0 (4.77)	–	–	26.1 (5.130)	–	–	–	–	–	–	25.2 (5.083)			25.1 (5.149)
Median	24.0 (15.2-46.4)	23.86 (16.4-44.4)	–	–	25.8	–	–	–	–	–	–	24.4 (14-47)			24.4 (14-47)
Clinical characteristics															
Duration of disease (years)															
Mean (SD)	6.7 ±4.0	6.1 ±3.6	5.8 (2.5)	5.9 (2.4)	5.3 (5.351)	12.9 (7.9)	12.1 (7.5)	–	–	16.8 (7.8)	16.2 (7.8)	4.2 (5.391)			not yet available
Median (range)	6.0 (1.1-32.9)	5.5 (0.9-23.8)	5.4 (1-20)	5.7 (2-15)	3.6 (3-7)	12.0 (1.4-44.4)	11.2 (0.4-39.4)	22 (4.55)	23 (4-55)	.	.	2.3 (0-33)			not yet available
EDSS score															
Mean	4.7 ±1.2	4.7 ±1.2	4.7 (1.03)	4.6 (1.03)	4.9 (1.203)	5.4 (1.1)	5.4 (1.0)					5.3 (1.074)	5.49 (0.99)	5.59 (0.94)	5.3 (1.061)
Median	4.5 (2.5-7.0)	4.5 (2.5-6.5)	4.5 (2.0-6.5)	4.5 (2.0-6.5)	4.5 (3-7)	6.0 (2.0-7.0)	6.0 (2.5-7.0)	6.0 (5.0-6.5)	6.0 (5.0-6.5)	6.0 (5.0-6.5)	6.0 (5.0-6.5)	6.0 (3,7)	6.0 (4.8-6.3)	6.0 (5.0-6.3)	6.0 (3-7)
No relapse in the year before screening	–	–	–	–	none	878 (79%)	416 (76%)	24 (4%)	25 (5%)			none			267 (100%)
No relapse in the 2 years before screening	–	–	–	–	2 (1.3%)	712 (64%)	343 (63%)	–	–			none			267 (100%)
Mean	–	–			0.01 (0.114)	0.7 (1.2)	0.7 (1.2)								
Median	–	–			0.0 (0-1)	0	0								
MRI characteristics															
Gadolinium-positive lesions on T1-no./total no. (%)															
Yes	133/484 (27.5)	60/243 (24.7)	46 (12.5)	61 (12.6)	27 (17.76)	237 (21)	114 (21)	–	–	114 (26)	96 (22)	49 (15.6)	93 (12.5)	49 (13.1)	18 (6.79)
No	351/484 (72.5)	183/243 (75.3)	290 (86.3)	423 (87.4)	125 (82.24)	833 (75)	415 (76)	–	–			264 (84.3)	661 (87.5)	328 (86.9)	247 (93.21)
Mean	1.2 (5.14)	0.6 (1.55)	–	–	0.4 (1.752)							0.3 (1.118)	–	–	
Median	0.0 (0.0-77.0)	0.0 (0.0-10.0)	–	–	0.0 (0-19)							0.0 (0-11)	50 (35-73) IQR	49 (33-75) IQR	
Volume of T2 lesions per patient (cm^3)															
Mean	12.7 ±15.1	10.9 ±13.0	9.4 ±10.1	10 ±13.0	not yet available	15.6 (16.2)	14.6 (15.6)	–	–	17.4 (17.6)	16.2 (16.4)				
Median	7.3 (0-90.3)	6.2 (0-81.1)	6.1 (1-52)	5,2	not yet available	10.2	9.9	–	–						
Normalized brain volume (cm^3)															
Mean	1462.9 ±84.0	1469.9 ±88.7	1490.9 (86.5)	1491.7 (84.9)	not yet available	1422 (86)	1425 (88)	–	–	1420.9 (82.8)	1425.8 (83.1)				
Median	1462.2 (1214.3-1711.1)	1464.5 (1216.3-1701.7)	1491.0 (1243-1725)	1498.0 (1206-1725)	not yet available	1421 (1136-1723)	1425 (1199-1691)	–	–						
Time since most recent relapse, years					2.4 (0.407)										
Treatment-naïve -no. (%)	433 (88.7)	214 (87.7)	272 (81.0)	372 (76.4)	41 (5.9)	245 (22)	114 (21)	–	–			202 (29.0)	205 (27.2)	89 (23.6)	172 (25)

PPMS Active and non-active SPMS Non-active or non-relapsing SPMS

1 Vietor, J., Gege, C., Stiller, T., Busch, R., Schallmayer, E., Kohlhof, H., Höfner, G., Pabel, J., Marschner, J.A. and Merk, D., 2023. Development of a potent Nurr1 agonist tool for in vivo applications. Journal of Medicinal Chemistry, 66(9), pp.6391-6402 https://doi.org/10.1021/acs.jmedchem.3c00415

2 Marschall M, Peelen E, Muller R, et al. IMU-838, a small molecule DHODH inhibitor in phase 2 clinical trial for multiple sclerosis, shows potent anti-EBV activity in cell- culture-based systems: potential additional benefits in multiple sclerosis treatment. ECTRIMS. 2021. ePoster P372. Multiple Sclerosis Journal. 2021;27(2_suppl): 134-740. doi:10.1177/13524585211044667

3 Disease subtype information are used as diagnosis entered by investigator at study entry. Data cut-off date from Interim Analysis: 16 Aug 2023

4 Data cut-off date: 11 Oct 2024