PERIPHERAL NERVE SOCIETY
2022 ANNUAL MEETING
14-17 MAY INTERCONTINENTAL MIAMI
MIAMI

REAL-WORLD EXPERIENCE WITH INOTERSEN AT CEPARM

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INTRODUCTION

Hereditary transthyretin amyloidosis (hATTR/ATTRv) is a severe, progressive and disabling disease, leading to multiorgan failure caused by the systemic accumulation of mutated TTR fibrils as amyloid into tissues, ultimately leading to death in untreated patients. TTR is primally synthetized by the liver.

Inotersen is an antisense drug (ASO) designed to degrade TTR mRNA in the liver, inhibiting TTR protein synthesis. The dose of inotersen is 300 mg SC once every week. Inotersen is approved to treat hATTR with polyneuropathy (PN) in several countries, including Brazil since October 2019.

Patients who completed Ionis 420915-CS2 and CS3 pivotal studies were enrolled in this post-approval (PSDS) real world practice study. The objective is to evaluate disease progression using standard measures as in daily practice at CEPARM, in patients treated with inotersen since Ionis 420915 main studies, and after at the post-approval real world practice period (PSDS), with a date of extraction as of October 2021.

METHODS

The following measures were evaluated at day one (D1) of inotersen treatment either during Ionis 420915-CS2 (double blind against placebo) or CS3 (open label active drug), and following an average of 67 months (55-76, SD 7.6) of treatment:

(PND) polyneuropathy disability scale, Coutinho stage of disease, (NIS) total neuropathy impairment score, (CNAP) amplitude of sural and peroneal compound nerve action potential, ECG, (IVS) echocardiogram intraventricular septum thickness, renal function, presence of cardiomyopathy, (NYHA) New York Heart Association classification for heart failure, (BMI) body mass index, and (KPS) Karnofsky performance status.

RESULTS

10 ATTRV30M subjects were included (6 men); mean age at disease onset of 43.9 years (31-67, SD 13.9); mean time to diagnosis of 20.1 months (3-48, SD12.1); mean disease duration at D1 of 3 years (1.5-6, SD1.4); mean age at D1 of 45.4 years (31-68, SD 13.9); 7 patients were early-onset (<50). (Table 1).

2 patients were previously treated by tafamidis (18 months and 24 months).

At D1 3 patients were at PND I, 5 at II, 2 at IIIA. At last evaluation (LE): 4 patients were at PND I, 3 at II, 1 at IIIA, and 2 at IV. At D1 8 patients were at Coutinho stage 1, and 2 at 2. At last evaluation: 7 at stage 1, 1 at stage 2 and 2 at stage 3. Amplitude of compound muscle action potential (CMAP) of peroneal nerve was unobtainable in 4 at D1 and in 6 at 67 months. Amplitude of compound sensory action potential of sural nerve (CSAP) was unobtainable in 7 out of 9 patients at D1 and in 8 out 9 patients at LE.

Both at D1 and at last evaluation, 3 patients had cardiomyopathy (CM) with 2 diagnosed with heart failure (NYHA 1 and 2). ECG at D1 was abnormal for 8 patients, mostly due to conduction abnormalities. At last evaluation, abnormalities persisted in 6 patients ; in 2 of those pacemakers were implanted, and 2 had low voltage. IVS thickness > 12mm was present in 4 patients at D1 and in only 2 at last visit. Renal function and protein excretion was maintained, with only 1 patient presenting GFR < 60 mL/min/1.73 m2 at D1 and at last evaluation. (Tables 2 and 3).

There was no case of glomerulonephritis and no platelet decrease grade 4. 2 patients paused drug for a total period of 5 and 2 months during one year follow-up.

At D1 mean NIS was 48.2 points (12-129.75, SD39.8); KPS was 77 (50-90, SD 12.5); BMI was 22.6 (14-30.5, SD 8.2). At last evaluation (October 2021), mean NIS was 52.6 (16-141, SD42.4); KPS was 77.7 (50-90, SD12); BMI was 24.8 (18.9-31.4, SD 4.9).

Figures 1 to 4 show evolution of BMI (IMC),KPS,NIS and PND from D1 of inotersen, baseline of PSDS (10/2020), 6 M (6 months 04/2021) and at 12 M (10/2021)

NIS progression of >10 points was identified in 4/9 patients assessed, 3 of whom had NIS of >50 at D1, late-onset, and mixed phenotype (PN and CM manifestations).

Patients who completed Ionis 420915-CS2 and CS3 pivotal studies were enrolled in this post-approval (PSDS) real world practice study. The objective is to evaluate disease progression using standard measures as in daily practice at CEPARM.

Neurological function based on NIS and PND was preserved during this period in most of the cases, as well as functionality (KPS), nutritional and cardiac aspects. No new safety sign was noted.

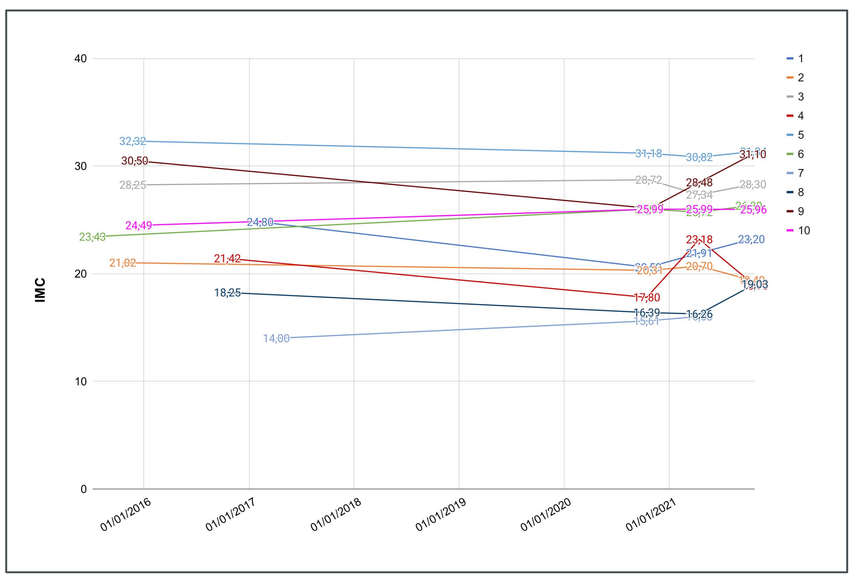
Based on these limited data, we conclude that treatment with inotersen was well tolerated and effective to treat patients during this period of 12 months of PSDS, in accordance with phase 3 trial results.

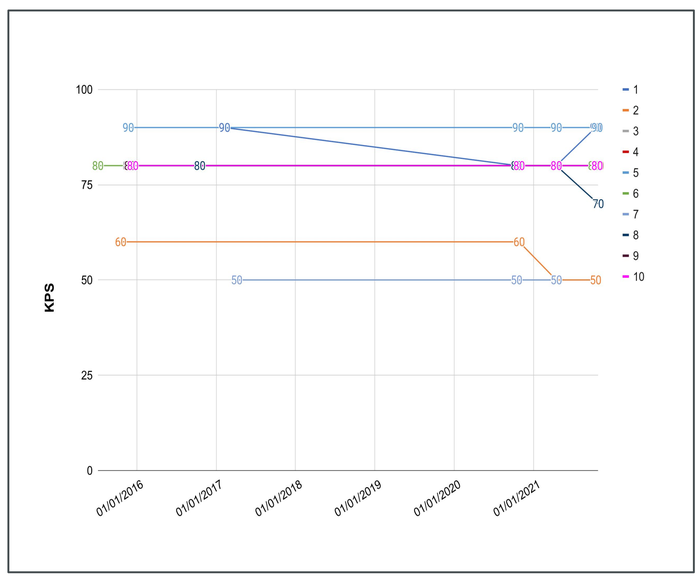
RESULTS

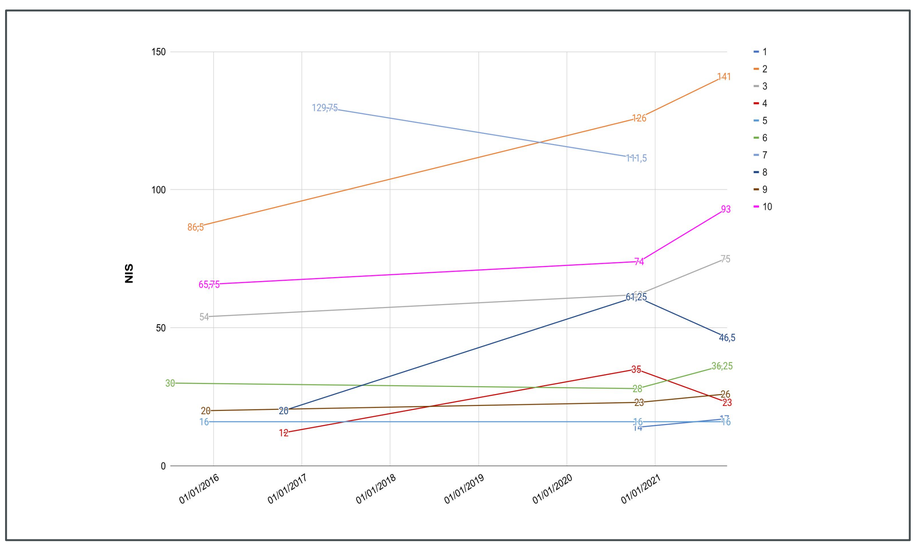
N	Mutation	Age at onset of disease (years)	Time from diagnosis (months)	Time from disease onset at D1 of inotersen (months)	D1 of inotersen	Age at D1 (years)	D1	Treatment time from D1 to last evaluation (months)
1	Val30Met	37	3	24	IONIS 420915-CS3	40	02/2017	57
2	Val30Met	67	12	24	IONIS 420915-CS2	68	10/2015	73
3	Val30Met	59	12	18	IONIS 420915-CS2	59	11/2015	72
4	Val30Met	34	24	36	IONIS 420915-CS3	35	10/2016	61
5	Val30Met	34	18	30	IONIS 420915-CS2	33	11/2015	72
6	Val30Met	35	24	36	IONIS 420915-CS2	35	07/2015	76
7	Val30Met	39	48	72	IONIS 420915-CS3	39	04/2017	55
8	Val30Met	31	12	60	IONIS 420915-CS3	31	10/2016	61
9	Val30Met	38	24	36	IONIS 420915-CS2	49	11/2015	72
10	Val30Met	65	24	30	IONIS 420915-CS2	65	12/2015	71
	Min	31	3	1.5		31		55
	Max	67	48	6		68		76
	Mean	43.9	20.1	3.05		45.4		67
	SD	13.96	12.16	1.40		13.90		7.63

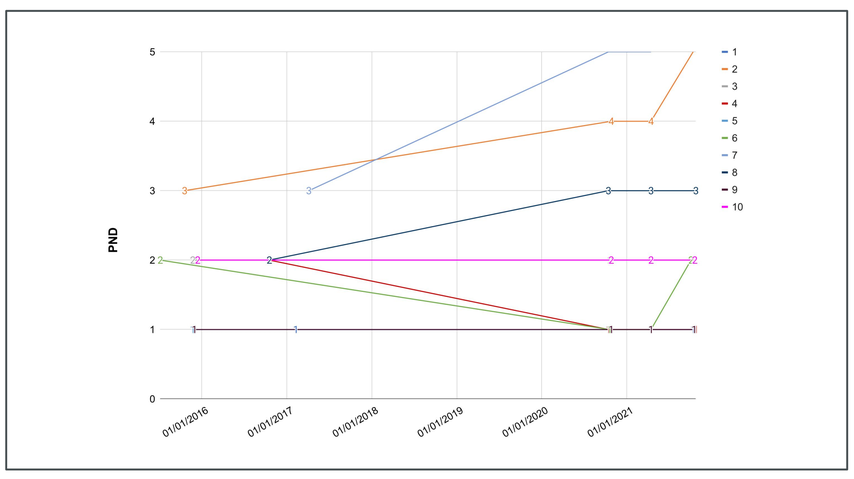
N	PND D1	Disease Stage D1	NIS D1	Sural nerve CSAP (µV) D1	Peroneal nerve CMAP (mV) D1	BMI D1	CM D1	Heart Failure D1	NYHA D1	ECG D1	IVS (mm) D1	EF % D1	Pro –BNP D1	KPS D!	GFR D1	ALB/ Crea D1	Ptn/Crea D1
1	I	1	NA			24.8	N	N	NA	extrassistoles	8	60		90	112	0.34	5
2	III A	2	86.5	0	0	21.2	Y	Y	I	AVB 1 st	13	NA	27	60	93	0.79	
3	II	1	54	0	0.1	28.25	Y	Y	II	RBB + AVB 1 st	15	NA	63	80	93	0.79	4
4	II	1	12	0.5	1,1	21.42	N	N	NA	N	9	NA		80	97	0.9	
5	I	1	26	6	3,5	32.32	N	N	NA	NS ST-T	10	86	12	90	125	0.34	12
6	II	1	30	0	0	23.43	N	N	NA	AVB 1 st LPHB	13	NA	4	80	96	1.2	7
7	III A	2	129.75	0	0	14	N	N	NA	AVB + flutter atrial	NA	NA		50	113	17.5	39
8	II	1	20	0	0	18.25	N	N	NA	AVB 1	9	69	32.8	80	124	0.45	6
9	I	1	20	0	0.6	30.5	N	N	NA	LAHB	10	NA	37	80	107	34.5	81
10	II	1	65.75	0	0.2	24.49	Y	N	NA	LAHB+ QS V1-3	14	71	50	80	59	0.24	10
		Min	12			14								50			
		Max	129.75			30.5								90			
		Mean	48.22			22.64								77			
		SD	39.88			8.27								12.51			

N	Date of last evaluation	PSDS	PND	Disease stage	NIS	Sural nerve CSAP (µV)	Peroneal nerve CMAP (mV)	BMI	CM	HF	NYHA	ECG	IVS	EF %	KPS	creatinin	ptn urin/24 horas	Ptn/ Crea
1	13/10/2021	12 M	I	1	17	0	2	23.2	N	N	NA	Low voltage	9	64	90	1.04	0.009	
2	13/10/2021	12M	IV	3	141	0	0	19.4	Y	Y	I	RBB + LAHB + AVB 1	18	60	50	0.62	0.1	0.008
3	18/10/2021	12M	II	1	75	0	0	28.3	Y	Y	II	AVB 2. Pacemaker 01/10/2021	11	67.8	80	NA	NA	NA
4	25/10/2021	12M	I	1	23	0	0	18.9	N	N	NA	N	10	64	80	1.05	0.22	NA
5	20/10/2021	12M	I	1	16	3.8	3.5	31.34	N	N	NA	Low voltage	9	63	90	0.85	0.08	0.2
6	04/10/2021	12M	II	1	36.25	0	0	26.3	N	N	NA	AVB 1 + LPHB (PR 314)	8	74	80	1.01	13.2	0.04
7	Remote	12M	IV	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.7	0.1	0.21
8	25/10/2021	12M	III A	2	46.5	0	0	19.03	N	N	NA	N	10	78	70	0.75	0.1	NA
9	18/10/2021	12M	I	1	26	0	0	31.1	N	N	NA	LAHB	10	68	80	0.75	0.11	NA
10	20/10/2021	12M	II	1	93	0	1.5	25.96	Y	N	NA	pacemaker	18	63	80	1.91	0.16	0.11
				Min	16			18,9							50			
				Max	141			31.34							90			
				Mean	52.63			24.83							77.77			
				SD	42.49			4.97							12			









CONCLUSIONS

This is a descriptive analysis in an effort to evaluate treatment response to a drug of difficult access in Brazil, considering the multiorgan nature of ATTR, and a real word practice scenario at CEPARM/ Federal University of Rio de Janeiro. Neurological function based on NIS and PND was preserved during this period in most of the cases, as well as functionality (KPS), nutritional and cardiac aspects. No new safety sign was noted. Based on these limited data, we conclude that treatment with inotersen was well tolerated and effective to treat patients during this period of 12 months of PSDS, in accordance with phase 3 trial results .Reference. Benson MD, et al. N Engl J Med. 2018;379:22-31.

Disclosures:

MWC: received honorarium from NHI, Prothena, FoldRx, Ionis Pharmaceuticals, Akcea Therapeutics, Pfizer, Alnylam Pharmaceuticals, PTC, SOBI, and Genzyme for travel expenses related to presentations at medical meetings, for acting as a principal investigator in clinical trials, and as a consultant member