Sponsor Versartis
Generic Drug Name Somavaratan (VRS-317)
Therapeutic Area of Trial Pediatric Growth Hormone Deficiency
Approved Indication None
Study Number 13VR3
Study Title An Open-Label, Long-Term Safety Study of A Long-acting Human Growth Hormone Somavaratan (VRS-317) in Children with Growth Hormone Deficiency The VISTA Study: Versartis Long-Term Safety Study of Somavaratan
Study Start/End Dates March 3, 2014 / November 17, 2017
Study Design/Methodology This study was a multi-center, open-label study to assess long-term somavaratan administration. It was open to pediatric growth hormone deficient (PGHD) subjects whom had completed a somavaratan study, as well as up to approximately 200 newly enrolling PGHD subjects who were either treatment naïve or were receiving daily rhGH therapy (switch subjects). All subjects received somavaratan 3.5 mg/kg twice monthly. The study was conducted at approximately 70 Pediatric Endocrinology centers in the United States, Canada, and Europe. Subjects were monitored for safety throughout their participation in the study. Safety was monitored by physical examination, inspection of injection sites, vital signs, clinical laboratory determinations (including fasting glucose, insulin, and lipids), 12-lead ECGs (obtained for new subjects and subjects not previously exposed to somavaratan), PK/PD assessments, and immunogenicity assessments. Adverse events (AEs) and concomitant medications (CMs) were captured. AEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE v 4.0). AEs were coded using the MedDRA dictionary and CMs using the WHO Drug dictionary.

An external Data and Safety Monitoring Board (DSMB) monitored the safety of the study subjects throughout the study duration. DSMB meetings occurred approximately every six months throughout the duration of the study. All available safety information was reviewed for any potential risk to subjects.

The study was discontinued early by sponsor decision due to the non-inferiority endpoint not being met in the Phase 3 study [Protocol 14VR4]). Duration of subject participation varied. This report contains only safety results, efficacy assessments were not conducted.

Centers

60 centers in 5 countries: Belgium (1), Canada (6), Poland (8), Sweden (1), USA (44)

Objectives

Primary Objective(s)
The primary objective of the study was to evaluate the safety of somavaratan during long-term treatment.

Secondary Objective(s)

The secondary objectives were to evaluate changes in pharmacodynamic responses (IGF-I and IGFBP-3), auxologic factors (height, weight, BMI, bone age, height velocity, and height standard deviation scores), metabolic parameters, pubertal development, and anti-drug antibody responses during long-term somavaratan treatment.

Test Product(s), Dose(s), and Mode(s) of Administration

Subjects received somavaratan 3.5 mg/kg twice per month (every 15 days ± 2 days) administered as subcutaneous bolus injection(s) in the abdomen, buttocks, thigh, or upper arm.

Comparison Product(s), Dose(s), and Mode(s) of Administration

No comparator products were used in this study.

Criteria for Evaluation – Safety

The following evaluations were performed to assess study eligibility and safety:

Physical examination including injection site(s) evaluation

Vital signs including sitting blood pressure, pulse rate, temperature and respiratory rate

Fasting laboratory tests: complete blood count, chemistry, hemoglobin A1c, thyroid function tests (Free T4 and TSH), insulin, glucose and lipids, urinalysis, and antibodies to somavaratan.

12-lead ECGs (for new subjects and subjects not previously exposed to somavaratan).

Adverse events (AEs)

Concomitant medications (CMs)

IGF-I SDS

Criteria for evaluation – Pharmacokinetics and Pharmacodynamics

PK: Somavaratan plasma concentrations

PD: IGF-I and IGFBP-3 concentrations and SDS at estimated peak and trough times

Criteria for evaluation – Efficacy

Standing height (by stadiometer, in triplicate measured without shoes)

Body weight (in light clothing and without shoes)

Bone Age at Day 1 and at each successive 12 month interval of somavaratan treatment (i.e. Months 12, 24, 36)

Tanner stage

Note: Efficacy, PK, and PD assessments were not completed and are not provided in this report.

Statistical Methods

Summaries of subject disposition, demographics, disease characteristics and response to dosing of study medication are provided for each treatment group. All summaries of continuous data are presented as means (SD), and/or with medians with min/max as appropriate. Count data are presented as number within each treatment group and % of subjects within each group.

Summaries of all adverse events (AEs), serious adverse events (SAEs) and Suspected, Unexpected Serious Adverse Reactions (SUSARs) are reported. The incidence of CTCAE Grade 3 or 4 adverse events are classified according to severity and relationship to study drug.

No formal hypothesis testing is planned for this open-label, long-term safety study. No efficacy analysis was conducted.

Four populations are described in the results section of this report:

1. 12VR2/13VR3 – These are subjects originally enrolled in the somavaratan Phase 2 study (Protocol 12VR2) that rolled over into the Open-Label, Long-Term Safety Study (Protocol 13VR3)

2. 14VR4/13VR3 – These are subjects originally enrolled in the somavaratan Phase 3 study (Protocol 14VR4) that rolled over into the Open-Label, Long-Term Safety Study (Protocol 13VR3) and includes subjects that received either daily rhGH or somavaratan in the original Phase 3 study.

3. 13VR3 New – These are naïve to rhGH treatment subjects that enrolled directly into the Open-Label, Long-Term Safety Study (Protocol 13VR3)

4. 13VR3 Switch – These are subjects that were receiving daily rhGH treatment that enrolled directly into the Open-Label, Long-Term Safety Study (Protocol 13VR3)

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria for Subjects Completing a Previous Somavaratan Study

1. Completion of a somavaratan clinical study in pediatric subjects with GHD.
2. Willing and able to comply with all study procedures.
3. Legally authorized representatives must be willing and able to give informed consent.

Inclusion Criteria for New Treatment Naïve Subjects

1. Chronological Age ≥ 3.0 years.
2. Pre-pubertal status: Absent breast development in girls, testicular volume < 4.0 mL in boys.
3. Diagnosis of GHD as documented by two or more GH stimulation test results ≤ 10.0 ng/mL. The use of prior GH stimulation test results is permitted providing the stimulatory agents, GH assay and test results are approved in writing by the medical monitor. In localities with different diagnostic criteria, any child meeting the GH stimulation test criteria described here will be considered eligible.
4. Normal thyroid function at Screening Visit in subjects not being treated for hypothyroidism. Subjects requiring thyroxine replacement must be considered adequately treated by the PI and Medical Monitor.
5. Normal adrenal function (morning cortisol and/or local stimulation test) at Screening Visit or within 6 months of the Screening Visit, in subjects not being treated for adrenal insufficiency. Subjects with adrenal insufficiency must receive glucocorticoid treatment for a minimum of 4 weeks before study drug administration.
6. Pathology relating to cause of GHD must be stable for at least 6 months prior to screening.
7. Legally authorized representatives must be willing and able to give informed consent.

Inclusion Criteria for Subjects Transitioning from Daily rhGH (Switch Subjects)

1. Subjects with GHD (diagnosed according to the current consensus guidelines) who are receiving treatment with daily rhGH.
2. Chronological Age ≥ 3.0 years.
3. Pre-pubertal status: Absent breast development in girls, testicular volume < 4.0 mL in boys.
4. Normal thyroid function at Screening Visit in subjects not being treated for hypothyroidism. Subjects requiring thyroxine replacement must be considered adequately treated by the PI and Medical Monitor.
5. Normal adrenal function (morning cortisol and/or local stimulation test) at Screening Visit or within 6 months of the Screening Visit, in subjects not being treated for adrenal insufficiency. Subjects with adrenal insufficiency must receive glucocorticoid treatment for a minimum of 4 weeks before study drug administration.
6. Pathology relating to cause of GHD must be stable for at least 6 months prior to screening.

7. Willingness to discontinue daily rhGH therapy.
8. Legally authorized representatives must be willing and able to give informed consent.

Exclusion Criteria for all Subjects:

1. Withdrawal from a somavaratan clinical study in pediatric subjects with GHD.
2. Current, significant disease (e.g., diabetes, cystic fibrosis, renal insufficiency). In all cases of concurrent disease, screening must be approved in writing by the medical monitor.
3. Chromosomal aneuploidy, significant gene mutations (other than those that cause GHD) or confirmed diagnosis of a named syndrome (e.g., Russell Silver, Prader Willi, Turner, etc.). Unconfirmed or suspected genetic variants will be considered individually.
4. Birth weight and/or birth length less than 5th percentile for gestational age using gestational age growth charts.
5. Prolonged daily (>14 days) use of anti-inflammatory doses of oral glucocorticoids.
6. Prior history of malignancy.
7. Treatment with an investigational drug in the 30 days prior to screening.
8. Known allergy to constituents of the study drug formulation.
9. Ocular findings suggestive of increased intracranial pressure and/or retinopathy at screening.
10. Significant spinal abnormalities including scoliosis, kyphosis, Chiari malformation, and spina bifida variants.
11. Significant abnormality in screening studies (as assessed by PI ***and*** medical monitor).
12. Current social conditions which would prevent completion of study activities (e.g., planned family move to a distant location).
13. History of pancreatitis or undiagnosed chronic abdominal pain.
14. History of spinal or total body irradiation.
15. Other pituitary hormone deficiencies that are not properly treated.
16. Unwillingness to provide consent for participation in all trial activities.

Demographics

	12VR2 /13VR3 (N= 60)	14VR4 /13VR3 (N=122)	13VR3 New (N=110)	13VR3 Switch (N= 93)	Total (n=385)
Country					
Belgium	0 (0.0%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Canada	0 (0.0%)	11 (9.0%)	0 (0.0%)	0 (0.0%)	11 (2.9%)
Poland	0 (0.0%)	29 (23.8%)	38 (34.5%)	20 (21.5%)	87 (22.6%)
Sweden	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
USA	60 (100%)	79 (64.8%)	72 (65.5%)	73 (78.5%)	284 (73.8%)
Region					
Europe	0 (0.0%)	32 (26.2%)	38 (34.5%)	20 (21.5%)	90 (23.4%)
North America	60 (100%)	90 (73.8%)	72 (65.5%)	73 (78.5%)	295 (76.6%)
Age (years)					
N	60	122	110	93	385
Median	8.0	7.0	8.0	9.0	8.0
Mean (SD)	7.9 (2.5)	7.6 (2.1)	7.9 (2.6)	8.6 (2.2)	7.9 (2.4)
Min, Max	3.0, 12	4.0, 12	3.0, 13	3.0, 12	3.0, 13
Gender					
Female	26 (43.3%)	50 (41.0%)	44 (40.0%)	25 (26.9%)	145 (37.7%)
Male	34 (56.7%)	72 (59.0%)	66 (60.0%)	68 (73.1%)	240 (62.3%)
Race					
American Indian or Alaska Native	1 (1.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Asian	4 (6.7%)	6 (4.9%)	4 (3.6%)	4 (4.3%)	18 (4.7%)
Black or African American	3 (5.0%)	1 (0.8%)	2 (1.8%)	1 (1.1%)	7 (1.8%)
Other	2 (3.3%)	5 (4.1%)	3 (2.7%)	2 (2.2%)	12 (3.1%)
White	50 (83.3%)	109 (89.3%)	101 (91.8%)	86 (92.5%)	346 (89.9%)
Ethnicity					
Hispanic or Latino	16 (26.7%)	10 (8.2%)	8 (7.3%)	5 (5.4%)	39 (10.1%)
Not Hispanic or Latino	44 (73.3%)	112 (91.8%)	102 (92.7%)	88 (94.6%)	346 (89.9%)

Subject Disposition

	12VR2 /13VR3	14VR4 /13VR3	13VR3 New	13VR3 Switch	Total
Total Subjects Screened					425
Total Subjects Randomized	60	122	112	96	390
Total Subjects Treated	60	122	110	93	385
Subjects Not a Screen Failure but not Treated	0	0	2	4	6
Subject Disposition n(%)					
Completed*	40 (66.7%)	118 (96.7%)	108 (98.2%)	86 (92.5%)	352 (91.4%)
Discontinued Early	20 (33.3%)	4 (3.3%)	4 (3.6%)	11 (11.8%)	39 (10.1%)
Reason for Discontinuation n(%)					
Adverse Event	1 (5.0%)	1 (25.0%)	0 (0.0%)	1 (9.1%)	3 (7.7%)
Lost to Follow-up	1 (5.0%)	1 (25.0%)	2 (50.0%)	1 (9.1%)	5 (12.8%)
Non-compliance with Study Drug	3 (15.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.7%)
Physician Decision	4 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (10.3%)
Protocol Violation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Terminated by Sponsor	2 (10.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	3 (7.7%)
Withdrawal by Subject	8 (40.0%)	1 (25.0%)	2 (50.0%)	7 (63.6%)	18 (46.2%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (5.0%)	1 (25.0%)	0 (0.0%)	1 (9.1%)	3 (7.7%)

* Note: These subjects completed the study based on the sponsor's decision to close the trial and came into clinic for a final study visit.

Anti-drug Antibody							
Visit	**Titer**	**Abnormal/Normal**	**12VR2 /13VR3 (N= 60)**	**14VR4 /13VR3 (N=122)**	**13VR3 New (N=110)**	**13VR3 Switch (N= 93)**	**Total (n=385)**
Screening	Titer	N	0	1	0	0	1
		Positive	0 (0.0%)	1 (100%)	0 (0.0%)	0 (0.0%)	1 (100%)
		N Missing Data	0	121	0	0	384
	NAB	N	0	1	0	0	1
		Positive	0 (0.0%)	1 (100%)	0 (0.0%)	0 (0.0%)	1 (100%)
		N Missing Data	0	121	0	0	384
Day 1	Titer	N	54	88	107	75	324
		Positive	39 (72.2%)	77 (87.5%)	20 (18.7%)	13 (17.3%)	149 (46.0%)
		Negative	15 (27.8%)	11 (12.5%)	87 (81.3%)	62 (82.7%)	175 (54.0%)
		N Missing Data	6	34	3	18	61
	NAB	N	33	87	107	75	302
		Positive	7 (21.2%)	29 (33.3%)	0 (0.0%)	0 (0.0%)	36 (11.9%)
		Negative	26 (78.8%)	58 (66.7%)	107 (100%)	75 (100%)	266 (88.1%)
		N Missing Data	27	35	3	18	83
Month 1	Titer	N	0	29	97	82	208
		Positive	0 (0.0%)	9 (31.0%)	30 (30.9%)	21 (25.6%)	60 (28.8%)
		Negative	0 (0.0%)	20 (69.0%)	67 (69.1%)	61 (74.4%)	148 (71.2%)
		N Missing Data	0	93	13	11	177
	NAB	N	0	28	97	82	207
		Positive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Negative	0 (0.0%)	28 (100%)	97 (100%)	82 (100%)	207 (100%)
		N Missing Data	0	94	13	11	178

Anti-drug Antibody (continued)							
Visit	**Titer**	**Abnormal/Normal**	**12VR2 /13VR3 (N= 60)**	**14VR4 /13VR3 (N=122)**	**13VR3 New (N=110)**	**13VR3 Switch (N= 93)**	**Total (n=385)**
Month 3	Titer	N	1	75	85	74	235
		Positive	0 (0.0%)	57 (76.0%)	62 (72.9%)	47 (63.5%)	166 (70.6%)
		Negative	1 (100%)	18 (24.0%)	23 (27.1%)	27 (36.5%)	69 (29.4%)
		N Missing Data	59	47	25	19	150
	NAB	N	1	75	85	74	235
		Positive	0 (0.0%)	13 (17.3%)	7 (8.2%)	7 (9.5%)	27 (11.5%)
		Negative	1 (100%)	62 (82.7%)	78 (91.8%)	67 (90.5%)	208 (88.5%)
		N Missing Data	59	47	25	19	150
Month 6	Titer	N	52	41	38	12	143
		Positive	35 (67.3%)	33 (80.5%)	32 (84.2%)	10 (83.3%)	110 (76.9%)
		Negative	17 (32.7%)	8 (19.5%)	6 (15.8%)	2 (16.7%)	33 (23.1%)
		N Missing Data	8	81	72	81	242
	NAB	N	47	41	38	12	138
		Positive	10 (21.3%)	13 (31.7%)	11 (28.9%)	4 (33.3%)	38 (27.5%)
		Negative	37 (78.7%)	28 (68.3%)	27 (71.1%)	8 (66.7%)	100 (72.5%)
		N Missing Data	13	81	72	81	247
Month 9	Titer	N	1	26	13	0	40
		Positive	1 (100%)	20 (76.9%)	10 (76.9%)	0 (0.0%)	31 (77.5%)
		Negative	0 (0.0%)	6 (23.1%)	3 (23.1%)	0 (0.0%)	9 (22.5%)
		N Missing Data	59	96	97	0	345
	NAB	N	1	26	13	0	40
		Positive	0 (0.0%)	6 (23.1%)	0 (0.0%)	0 (0.0%)	6 (15.0%)
		Negative	1 (100%)	20 (76.9%)	13 (100%)	0 (0.0%)	34 (85.0%)
		N Missing Data	59	96	97	0	345

Anti-drug Antibody (continued)							
Visit	**Titer**	**Abnormal/Normal**	**12VR2 /13VR3 (N= 60)**	**14VR4 /13VR3 (N=122)**	**13VR3 New (N=110)**	**13VR3 Switch (N= 93)**	**Total (n=385)**
Month 12	Titer	N	43	6	0	0	49
		Positive	31 (72.1%)	6 (100%)	0 (0.0%)	0 (0.0%)	37 (75.5%)
		Negative	12 (27.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (24.5%)
		N Missing Data	17	116	0	0	336
	NAB	N	37	6	0	0	43
		Positive	2 (5.4%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	5 (11.6%)
		Negative	35 (94.6%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	38 (88.4%)
		N Missing Data	23	116	0	0	342
Month 15	Titer	N	4	2	0	0	6
		Positive	4 (100%)	2 (100%)	0 (0.0%)	0 (0.0%)	6 (100%)
		N Missing Data	56	120	0	0	379
	NAB	N	4	2	0	0	6
		Positive	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)
		Negative	4 (100%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	5 (83.3%)
		N Missing Data	56	120	0	0	379
Month 18	Titer	N	46	0	0	0	46
		Positive	33 (71.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	33 (71.7%)
		Negative	13 (28.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (28.3%)
		N Missing Data	14	0	0	0	339
	NAB	N	45	0	0	0	45
		Positive	7 (15.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (15.6%)
		Negative	38 (84.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	38 (84.4%)
		N Missing Data	15	0	0	0	340

Anti-drug Antibody (continued)							
Visit	**Titer**	**Abnormal/Normal**	**12VR2 /13VR3 (N= 60)**	**14VR4 /13VR3 (N=122)**	**13VR3 New (N=110)**	**13VR3 Switch (N= 93)**	**Total (n=385)**
Month 21	Titer	N	42	0	0	0	42
		Positive	30 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	30 (71.4%)
		Negative	12 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (28.6%)
		N Missing Data	18	0	0	0	343
	NAB	N	42	0	0	0	42
		Positive	2 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.8%)
		Negative	40 (95.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	40 (95.2%)
		N Missing Data	18	0	0	0	343
Month 24	Titer	N	48	0	0	0	48
		Positive	32 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (66.7%)
		Negative	16 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (33.3%)
		N Missing Data	12	0	0	0	337
	NAB	N	48	0	0	0	48
		Positive	13 (27.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (27.1%)
		Negative	35 (72.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (72.9%)
		N Missing Data	12	0	0	0	337
Month 27	Titer	N	46	0	0	0	46
		Positive	32 (69.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (69.6%)
		Negative	14 (30.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (30.4%)
		N Missing Data	14	0	0	0	339
	NAB	N	46	0	0	0	46
		Positive	4 (8.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (8.7%)
		Negative	42 (91.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	42 (91.3%)
		N Missing Data	14	0	0	0	339

Anti-drug Antibody (continued)							
Visit	**Titer**	**Abnormal/Normal**	**12VR2 /13VR3 (N= 60)**	**14VR4 /13VR3 (N=122)**	**13VR3 New (N=110)**	**13VR3 Switch (N= 93)**	**Total (n=385)**
Month 30	Titer	N	42	0	0	0	42
		Positive	26 (61.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (61.9%)
		Negative	16 (38.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (38.1%)
		N Missing Data	18	0	0	0	343
	NAB	N	42	0	0	0	42
		Positive	7 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (16.7%)
		Negative	35 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (83.3%)
		N Missing Data	18	0	0	0	343
Month 33	Titer	N	42	0	0	0	42
		Positive	27 (64.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	27 (64.3%)
		Negative	15 (35.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (35.7%)
		N Missing Data	18	0	0	0	343
	NAB	N	42	0	0	0	42
		Positive	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)
		Negative	41 (97.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	41 (97.6%)
		N Missing Data	18	0	0	0	343
Month 36	Titer	N	42	0	0	0	42
		Positive	28 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (66.7%)
		Negative	14 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (33.3%)
		N Missing Data	18	0	0	0	343
	NAB	N	42	0	0	0	42
		Positive	8 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (19.0%)
		Negative	34 (81.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	34 (81.0%)
		N Missing Data	18	0	0	0	343

Anti-drug Antibody (continued)							
Visit	**Titer**	**Abnormal/Normal**	**12VR2 /13VR3 (N= 60)**	**14VR4 /13VR3 (N=122)**	**13VR3 New (N=110)**	**13VR3 Switch (N= 93)**	**Total (n=385)**
Month 39	Titer	N	40	0	0	0	40
		Positive	25 (62.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	25 (62.5%)
		Negative	15 (37.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (37.5%)
		N Missing Data	20	0	0	0	345
	NAB	N	40	0	0	0	40
		Positive	3 (7.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.5%)
		Negative	37 (92.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	37 (92.5%)
		N Missing Data	20	0	0	0	345
Month 42	Titer	N	26	0	0	0	26
		Positive	17 (65.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (65.4%)
		Negative	9 (34.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (34.6%)
		N Missing Data	34	0	0	0	359
	NAB	N	26	0	0	0	26
		Positive	8 (30.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (30.8%)
		Negative	18 (69.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (69.2%)
		N Missing Data	34	0	0	0	359
Month 48	Titer	N	1	0	0	0	1
		Positive	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
		N Missing Data	59	0	0	0	384
	NAB	N	1	0	0	0	1
		Negative	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
		N Missing Data	59	0	0	0	384

Anti-drug Antibody (continued)							
Visit	**Titer**	**Abnormal/Normal**	**12VR2 /13VR3 (N= 60)**	**14VR4 /13VR3 (N=122)**	**13VR3 New (N=110)**	**13VR3 Switch (N= 93)**	**Total (n=385)**
Termination	Titer	N	42	111	99	88	340
		Positive	32 (76.2%)	95 (85.6%)	82 (82.8%)	65 (73.9%)	274 (80.6%)
		Negative	10 (23.8%)	16 (14.4%)	17 (17.2%)	23 (26.1%)	66 (19.4%)
		N Missing Data	18	11	11	5	45
	NAB	N	38	111	98	88	335
		Positive	10 (26.3%)	31 (27.9%)	27 (27.6%)	26 (29.5%)	94 (28.1%)
		Negative	28 (73.7%)	80 (72.1%)	71 (72.4%)	62 (70.5%)	241 (71.9%)
		N Missing Data	22	11	12	5	50

Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Occurring in ≥ 1% of Total Subjects)

System Organ Class Preferred Term	12VR2 /13VR3 (N=60)	14VR4 /13VR3 (N=122)	13VR3 New (N=110)	13VR3 Switch (N=93)	Total (n=385)
Total Number of AEs	519	200	202	125	1,046
Total Number of Subjects with at least one AE	55 (91.7%)	61 (50.0%)	62 (56.4%)	55 (59.1%)	233 (60.5%)
Infections and infestations	35 (58.3%)	22 (18.0%)	23 (20.9%)	23 (24.7%)	103 (26.8%)
Upper respiratory tract infection	12 (20.0%)	4 (3.3%)	8 (7.3%)	10 (10.8%)	34 (8.8%)
Nasopharyngitis	11 (18.3%)	2 (1.6%)	5 (4.5%)	1 (1.1%)	19 (4.9%)
Pharyngitis streptococcal	7 (11.7%)	2 (1.6%)	4 (3.6%)	4 (4.3%)	17 (4.4%)
Sinusitis	6 (10.0%)	1 (0.8%)	0 (0.0%)	3 (3.2%)	10 (2.6%)
Otitis media	4 (6.7%)	3 (2.5%)	2 (1.8%)	0 (0.0%)	9 (2.3%)
Bronchitis	3 (5.0%)	2 (1.6%)	1 (0.9%)	0 (0.0%)	6 (1.6%)
Ear infection	2 (3.3%)	1 (0.8%)	0 (0.0%)	2 (2.2%)	5 (1.3%)
Gastroenteritis viral	4 (6.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	5 (1.3%)
Influenza	4 (6.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	5 (1.3%)
Cellulitis	0 (0.0%)	0 (0.0%)	1 (0.9%)	3 (3.2%)	4 (1.0%)
Molluscum contagiosum	2 (3.3%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	4 (1.0%)
Otitis externa	1 (1.7%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	4 (1.0%)
Pneumonia	2 (3.3%)	1 (0.8%)	1 (0.9%)	0 (0.0%)	4 (1.0%)
Urinary tract infection	2 (3.3%)	1 (0.8%)	1 (0.9%)	0 (0.0%)	4 (1.0%)
Viral infection	4 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.0%)
General disorders and administration site conditions	28 (46.7%)	25 (20.5%)	13 (11.8%)	21 (22.6%)	87 (22.6%)
Injection site pain	9 (15.0%)	13 (10.7%)	7 (6.4%)	12 (12.9%)	41 (10.6%)
Pyrexia	15 (25.0%)	7 (5.7%)	4 (3.6%)	4 (4.3%)	30 (7.8%)
Injection site erythema	1 (1.7%)	3 (2.5%)	2 (1.8%)	3 (3.2%)	9 (2.3%)
Injection site haematoma	2 (3.3%)	3 (2.5%)	4 (3.6%)	0 (0.0%)	9 (2.3%)
Injection site swelling	1 (1.7%)	0 (0.0%)	2 (1.8%)	1 (1.1%)	4 (1.0%)
Nervous system disorders	23 (38.3%)	9 (7.4%)	14 (12.7%)	12 (12.9%)	58 (15.1%)
Headache	22 (36.7%)	9 (7.4%)	13 (11.8%)	11 (11.8%)	55 (14.3%)
Gastrointestinal disorders	25 (41.7%)	12 (9.8%)	12 (10.9%)	6 (6.5%)	55 (14.3%)
Vomiting	12 (20.0%)	6 (4.9%)	7 (6.4%)	3 (3.2%)	28 (7.3%)
Abdominal pain	5 (8.3%)	3 (2.5%)	1 (0.9%)	1 (1.1%)	10 (2.6%)
Diarrhoea	4 (6.7%)	2 (1.6%)	3 (2.7%)	1 (1.1%)	10 (2.6%)
Nausea	3 (5.0%)	3 (2.5%)	3 (2.7%)	0 (0.0%)	9 (2.3%)
Abdominal pain upper	4 (6.7%)	2 (1.6%)	1 (0.9%)	1 (1.1%)	8 (2.1%)
Constipation	2 (3.3%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	4 (1.0%)
Oral pain	3 (5.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	4 (1.0%)
Investigations	15 (25.0%)	9 (7.4%)	20 (18.2%)	4 (4.3%)	48 (12.5%)
IGF-I increased	5 (8.3%)	1 (0.8%)	8 (7.3%)	1 (1.1%)	15 (3.9%)
ALT increased	0 (0.0%)	1 (0.8%)	4 (3.6%)	0 (0.0%)	5 (1.3%)
AST increased	0 (0.0%)	1 (0.8%)	4 (3.6%)	0 (0.0%)	5 (1.3%)
WBC count decreased	2 (3.3%)	1 (0.8%)	2 (1.8%)	0 (0.0%)	5 (1.3%)
Blood TSH increased	2 (3.3%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	4 (1.0%)
Hepatic enzyme increased	1 (1.7%)	0 (0.0%)	2 (1.8%)	1 (1.1%)	4 (1.0%)

Treatment Emergent Adverse Events by System Organ Class and Preferred Term (continued) (Occurring in ≥ 1% of Total Subjects)

System Organ Class Preferred Term	12VR2 /13VR3 (N=60)	14VR4 /13VR3 (N=122)	13VR3 New (N=110)	13VR3 Switch (N=93)	Total (n=385)
Investigations (continued)	15 (25.0%)	9 (7.4%)	20 (18.2%)	4 (4.3%)	48 (12.5%)
IGF-I decreased	1 (1.7%)	1 (0.8%)	2 (1.8%)	0 (0.0%)	4 (1.0%)
Thyroxine free decreased	2 (3.3%)	1 (0.8%)	1 (0.9%)	0 (0.0%)	4 (1.0%)
Respiratory, thoracic and mediastinal disorders	26 (43.3%)	12 (9.8%)	5 (4.5%)	4 (4.3%)	47 (12.2%)
Cough	16 (26.7%)	5 (4.1%)	3 (2.7%)	1 (1.1%)	25 (6.5%)
Nasal congestion	8 (13.3%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	9 (2.3%)
Oropharyngeal pain	4 (6.7%)	3 (2.5%)	0 (0.0%)	1 (1.1%)	8 (2.1%)
Rhinitis allergic	4 (6.7%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	5 (1.3%)
Musculoskeletal and connective tissue disorders	18 (30.0%)	7 (5.7%)	10 (9.1%)	11 (11.8%)	46 (11.9%)
Pain in extremity	7 (11.7%)	4 (3.3%)	4 (3.6%)	5 (5.4%)	20 (5.2%)
Arthralgia	11 (18.3%)	1 (0.8%)	2 (1.8%)	4 (4.3%)	18 (4.7%)
Back pain	3 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	4 (1.0%)
Myalgia	2 (3.3%)	1 (0.8%)	1 (0.9%)	0 (0.0%)	4 (1.0%)
Injury, poisoning and procedural complications	12 (20.0%)	8 (6.6%)	8 (7.3%)	8 (8.6%)	36 (9.4%)
Laceration	2 (3.3%)	2 (1.6%)	2 (1.8%)	1 (1.1%)	7 (1.8%)
Ligament sprain	2 (3.3%)	2 (1.6%)	2 (1.8%)	1 (1.1%)	7 (1.8%)
Skin and subcutaneous tissue disorders	11 (18.3%)	3 (2.5%)	8 (7.3%)	4 (4.3%)	26 (6.8%)
Rash	4 (6.7%)	2 (1.6%)	3 (2.7%)	0 (0.0%)	9 (2.3%)
Eczema	2 (3.3%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	4 (1.0%)
Immune system disorders	6 (10.0%)	3 (2.5%)	4 (3.6%)	3 (3.2%)	16 (4.2%)
Multiple allergies	4 (6.7%)	2 (1.6%)	2 (1.8%)	0 (0.0%)	8 (2.1%)
Hypersensitivity	1 (1.7%)	0 (0.0%)	2 (1.8%)	2 (2.2%)	5 (1.3%)
Eye disorders	9 (15.0%)	1 (0.8%)	2 (1.8%)	2 (2.2%)	14 (3.6%)
Conjunctivitis	4 (6.7%)	1 (0.8%)	0 (0.0%)	2 (2.2%)	7 (1.8%)
Metabolism and nutrition disorders	6 (10.0%)	2 (1.6%)	4 (3.6%)	1 (1.1%)	13 (3.4%)
Vitamin D deficiency	4 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.0%)
Blood and lymphatic system disorders	2 (3.3%)	1 (0.8%)	4 (3.6%)	3 (3.2%)	10 (2.6%)
Lymphadenopathy	2 (3.3%)	1 (0.8%)	3 (2.7%)	2 (2.2%)	8 (2.1%)
Psychiatric disorders	2 (3.3%)	3 (2.5%)	3 (2.7%)	2 (2.2%)	10 (2.6%)
Attention deficit/hyperactivity disorder	2 (3.3%)	2 (1.6%)	2 (1.8%)	0 (0.0%)	6 (1.6%)

Adverse Events of Interest

System Organ Class Preferred Term	12VR2 /13VR3 (N= 60)	14VR4 /13VR3 (N=122)	13VR3 New (N=110)	13VR3 Switch (N= 93)	Total (n=385)
Total Number of Special Interest AEs	105	37	33	34	209
Total Number of Subjects with at least one Special Interest AE	26 (43.3%)	21 (17.2%)	23 (20.9%)	23 (24.7%)	93 (24.2%)
Nervous system disorders	22 (36.7%)	9 (7.4%)	13 (11.8%)	11 (11.8%)	55 (14.3%)
Headache	22 (36.7%)	9 (7.4%)	13 (11.8%)	11 (11.8%)	55 (14.3%)
General disorders and administration site conditions	10 (16.7%)	16 (13.1%)	8 (7.3%)	14 (15.1%)	48 (12.5%)
Injection site pain	9 (15.0%)	13 (10.7%)	7 (6.4%)	12 (12.9%)	41 (10.6%)
Injection site erythema	1 (1.7%)	3 (2.5%)	2 (1.8%)	3 (3.2%)	9 (2.3%)
Immune system disorders	1 (1.7%)	0 (0.0%)	2 (1.8%)	2 (2.2%)	5 (1.3%)
Hypersensitivity	1 (1.7%)	0 (0.0%)	2 (1.8%)	2 (2.2%)	5 (1.3%)

Grade 3 or Higher Treatment Emergent Adverse Events

Preferred Term	12VR2 /13VR3 (N= 60)	14VR4 /13VR3 (N=122)	13VR3 New (N=110)	13VR3 Switch (N= 93)	Total (n=385)
Total Number of AEs Greater than or Equal to Grade 3	3	3	4	0	10
Total Number of Subjects with at least one AE Greater than or Equal to Grade 3	3 (5.0%)	2 (1.6%)	2 (1.8%)	0 (0.0%)	7 (1.8%)
Abscess neck	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
Injection site erythema	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
Injection site pain	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
Injection site swelling	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
Laceration	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Pneumonia	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Pneumothorax	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Testicular torsion	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Wrist fracture	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

Adverse Events Leading to Discontinuation

System Organ Class Preferred Term	12VR2 /13VR3 (N= 60)	14VR4 /13VR3 (N=122)	13VR3 New (N=110)	13VR3 Switch (N= 93)	Total (n=385)
Total Number of AEs Leading to Discontinuation of Study Drug	3	4	0	1	8
Total Number of Subjects with at least one AE Leading to Discontinuation of Study Drug	1 (1.7%)	2 (1.6%)	0 (0.0%)	1 (1.1%)	4 (1.0%)
General disorders and administration site conditions	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	2 (0.5%)
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.3%)
Injection site pain	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Infections and infestations	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Abscess neck	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Arthralgia	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Musculoskeletal chest pain	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Pneumothorax	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Vascular disorders	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Jugular vein thrombosis	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

Serious Adverse Events

System Organ Class Preferred Term	12VR2 /13VR3 (N=60)	14VR4 /13VR3 (N=122)	13VR3 New (N=110)	13VR3 Switch (N=93)	Total (n=385)
Total Number of SAEs	2	3	0	0	5
Total Number of Subjects with at least one SAE	2 (3.3%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	4 (1.0%)
Infections and infestations	1 (1.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Abscess neck	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Pneumonia	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Nervous system disorders	1 (1.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Convulsion	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Seizure like phenomena	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Pneumothorax	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

Note: All Serious Adverse Events were considered unrelated to somavaratan treatment

Other Relevant Findings
None

Date of Clinical Study Report

March 1, 2018

The study was conducted in accordance with the Declaration of Helsinki and its revisions as well as with the valid national laws of the participating countries, with the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (E6) issued in July 1996, and with the Commission Directives 1991/507/EEC, 2001/20/EC, 2005/28/EC and 2001/83/EC.

We certify that to the best of our knowledge the information submitted in this report are truthful and accurate.

Signature Approval

2 MAR 18

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Versartis, Inc.

1/MARCH/2018

Eric Humphriss, MBA
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