Sponsor

Novartis

Generic Drug Name

SAF312

Therapeutic Area of Trial

Neurogenic detrusor overactivity

Approved Indication

Investigational

Protocol Number

CSAF312A2202

Title

A multi-center, double-blind, randomized, placebo-controlled, cross-over study to evaluate the efficacy, safety and tolerability of SAF312 in subjects with neurogenic detrusor overactivity due to spinal cord lesions who are inadequately managed by antimuscarinic therapy

Study Phase

Phase II

Study Start/End Dates

30-Mar-2012 to 26-Sep-2012

Early termination date: 18-Dec-2012. The study was terminated per protocol after identifying a suspected serious adverse reaction (SUSAR) in the second patient enrolled and exposed to SAF312. No further patients were enrolled.

Study Design/Methodology

Exploratory, multi-centered, randomized, double-blinded, placebo-controlled, cross-over study in 36 subjects with spinal cord lesions and confirmed neurogenic detrusor overactivity who were inadequately managed by antimuscarinic therapy. A 2 part study: proof of efficacy and an optional second part to examine the study medication at a lower dose. The first part of the study (proof of efficacy trial) consisted of two treatment periods, each of one week (Day 1 to Day 7) of treatment in a b.i.d. (two times a day) regimen of SAF312 or placebo.
Between the treatment periods, there was a wash-out period of at least 7 days. In Period 1, half of the subjects were planned to receive SAF312 25 mg b.i.d. The other half of the subjects were to receive matching placebo. For Period 2, after the wash-out period of at least one week, subjects were planned to be crossed-over to receive treatment, comparable to Period 1.

Centers

2 centers in 2 countries

Publication

None

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

Hard gelatin capsules of SAF312 25mg or matching placebo capsules were administered twice daily (bid) orally for one week each, with a washout period of at least 7 days between treatments.

Statistical Methods

The primary endpoint (maximum cystometric capacity (MCC)) was planned to be analyzed by mixed effect model with Baseline as covariate, treatment and period as fixed effects and patient as random effect. However, no statistical analysis was performed since the study was terminated early with only 2 patients and only 1 out of these 2 patients had efficacy observations for post Baseline visit. Therefore only the listing of MCC variables was produced for the primary endpoint. The secondary PD endpoints were planned to be summarized by treatment and visit. Due to the same reason only the listing of catheterization and incontinence was produced for the secondary PD endpoints. PK evaluations were done by non-compartmental analysis. Available PK parameters and concentrations were listed.
Safety data were summarized by treatment over time.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Males or female patients 18-65 years of age with an established diagnosis of Neurogenic Detrusor Overactivity as result of a spinal cord lesions (*e.g.*, traumatic, vascular, postsurgical) with complete or incomplete lesions. The neurological injuries required to have occurred at least six (6) months prior to screening.
- Neurogenic detrusor overactivity, demonstrated by bladder volume below the normal bladder capacity (< 400 mL) as measured at first involuntary detrusor contraction (threshold volume) during filling cystometry at Baseline.
- Subjects were required to have been inadequately managed through antimuscarinic therapy prior to screening. Inadequate management via antimuscarinic therapy after at least one month of treatment of patients, free of acute urinary tract infection, is considered as follows:
    - detrusor overactivity demonstrated by bladder volume below the normal bladder capacity (< 400 mL) as measured at first involuntary detrusor contraction (threshold volume) during filling cystometry at Baseline and/or
    - incontinence related to detrusor overactivity and/or
    - intolerable side-effects in the opinion of the subject and/or Investigator (*e.g.*, elevation of intraocular pressure, photophobia or blurring of vision, tachycardia, constipation, reflux disease, dry mouth, dizziness, restlessness)

Exclusion criteria

- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer; or longer, if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations. Usage of intravesical antimuscarinics, *e.g.*, oxybutynine instilled intravesically, at stable dosages were permitted in accordance with Inclusion criteria.
- Subject with current or ongoing evidence of:
    - chronic inflammation such as interstitial cystitis which was not adequately treated,

- bladder stones, hematuria of unknown origin, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs.

- Subjects with a history or evidence of any pelvic or genitourinary tract anomalies (*e.g.*, ectopic ureters, fistulas) including surgery or bladder disease other than detrusor overactivity that may have impacted on bladder function with the exception of bladder stones (>6 months ago) and stress incontinence, uterine prolapse, rectocele, or cystocele (>1 year ago) from screening.
- Subjects with an acute urinary tract infection (UTI). A UTI was defined as either a positive urine culture result with a bacteriuria count >105 CFU/mL conjoint with leukocyturia (pyuria) defined as >100 leukocytes per mm3 of uncentrifuged urine (in a haemocytometer) at screening or a positive urine culture that, in the Investigator`s opinion, required antibiotic therapy.
- Use of other treatment intended to treat overactive bladder symptoms including electrostimulation therapy, botulinum toxin, capsaicin and/or resiniferatoxin therapy in the six (6) months prior to the commencement of the study.
- Use of antidepressants or muscle relaxants which have not been administered at a constant dose for at least 1 month prior to the commencement of the study.

Participant Flow

	Sequence AB N=1	Sequence BA N=1	Total N=2
Patients			
Completed		1 (100.0%)	1 (50.0%)
Discontinued	1 (100.0%)		1 (50.0%)
Adverse Event(s)	1 (100.0%)		1 (50.0%)

Sequence AB, Period 1: SAF312 25mg b.i.d. Period 2: Placebo; Sequence BA, Period 1: Placebo Period 2: SAF312 25mg b.i.d.

Baseline Characteristics

		Sequence AB N=1	Sequence BA N=1
Gender - n	Male	1	1
Predominant race - n	Caucasian	1	1
Ethnicity - n	Other	1	1
BMI (kg/m^2)		26.5	24.4

Sequence AB, Period 1: SAF312 25mg b.i.d. Period 2: Placebo; Sequence BA, Period 1: Placebo Period 2: SAF312 25mg b.i.d.
BMI = body mass index

Outcome Measures

Primary Outcome Result(s)

Change from baseline of maximum cystometric capacity (MCC)

MCC (mL)	Sequence AB N=1	Sequence BA N=1
Study Day		
Baseline	267.00	300.00
P1 D7	-	380.00
P2 D7	-	310.00

Sequence AB, Period 1: SAF312 25mg b.i.d. Period 2: Placebo; Sequence BA, Period 1: Placebo Period 2: SAF312 25mg b.i.d.

Secondary Outcome Result(s)

Change from baseline of other cystometry variables including bladder volume at first involuntary detrusor contraction (VFDC), *threshold volume, d*etrusor pressure of first involuntary detrusor contraction (PFDC), *threshold pressure,* instilled volume at first leak (VLeak), detrusor pressure at first leak (PLeak), volume/detrusor pressure at first sensation (VSens/ PSens), volume/detrusor pressure at first desire to void (VDesire / PDesire), maximum detrusor pressure during filling/storage phase (PMax), bladder wall compliance.

Treatment sequence	Center/ Subject	Visit	Study day	Date	Time	Hours post dose	Parameter	Result	Unit
BA		Baseline 1					Maximum cystometric capacity	300.00	mL
							Bladder volume of first detrusor contraction	260.00	mL
							Instilled volume at first leak	235.00	mL
							Detrusor pressure at first leak	30.00	cm H2O
							Detrusor pressure at first sensation	7.00	cm H2O
							Detrusor pressure at first desire to void	20.00	cm H2O
							Maximum detrusor pressure during filling/storage phase	37.00	cm H2O
							Maximum bladder volume	300.00	mL
							Pressure associated with maximum bladder volume	25.00	cm H2O
							Baseline bladder volume	0.00	mL
							Baseline bladder pressure	20.00	cm H2O
							Detrusor pressure at first (involuntary) detrusor contraction	19.00	cm H2O
							Volume at first sensation	57.00	mL
							Volume at first desire to void	279.00	mL
							Filling rate	20.00	mL/min
		P1 D7					Maximum cystometric capacity	380.00	mL
							Bladder volume of first detrusor contraction	350.00	mL
							Instilled volume at first leak	375.00	mL
							Detrusor pressure at first leak	28.00	cm H2O
							Detrusor pressure at first sensation	2.00	cm H2O
							Detrusor pressure at first desire to void	3.00	cm H2O
							Maximum detrusor pressure during filling/storage phase	38.00	cm H2O
							Maximum bladder volume	380.00	mL

BA	P1 D7	Pressure associated with maximum bladder volume	21.00 cm H2O
		Baseline bladder volume	0.00 mL
		Baseline bladder pressure	22.00 cm H2O
		Detrusor pressure at first (involuntary) detrusor contraction	13.00 cm H2O
		Volume at first sensation	120.00 mL
		Volume at first desire to void	193.00 mL
		Filling rate	20.00 mL/min
	P2 D7	Maximum cystometric capacity	310.00 mL
		Bladder volume of first detrusor contraction	300.00 mL
		Instilled volume at first leak	310.00 mL
		Detrusor pressure at first leak	40.00 cm H2O
		Detrusor pressure at first sensation	3.00 cm H2O
		Detrusor pressure at first desire to void	3.00 cm H2O
		Maximum detrusor pressure during filling/storage phase	43.00 cm H2O
		Maximum bladder volume	310.00 mL
		Pressure associated with maximum bladder volume	43.00 cm H2O
		Baseline bladder volume	0.00 mL
		Baseline bladder pressure	24.00 cm H2O
		Detrusor pressure at first (involuntary) detrusor contraction	45.00 cm H2O
		Volume at first sensation	247.00 mL
		Volume at first desire to void	250.00 mL
		Filling rate	20.00 mL/min
AB	Baseline 1	Maximum cystometric capacity	267.00 mL
AB	Baseline 1	Bladder volume of first detrusor contraction	208.00 mL
		Instilled volume at first leak	267.00 mL
		Detrusor pressure at first leak	65.00 cm H2O
		Detrusor pressure at first sensation	7.00 cm H2O
		Detrusor pressure at first desire to void	1.00 cm H2O
		Maximum detrusor pressure during filling/storage phase	70.00 cm H2O
		Maximum bladder volume	267.00 mL
		Pressure associated with maximum bladder volume	11.00 cm H2O
		Baseline bladder volume	0.00 mL
		Baseline bladder pressure	0.00 cm H2O
		Detrusor pressure at first (involuntary) detrusor contraction	18.00 cm H2O
		Volume at first sensation	200.00 mL
		Volume at first desire to void	204.00 mL
		Filling rate	20.00 mL/min

Sequence AB, Period 1: SAF312 25mg b.i.d. Period 2: Placebo; Sequence BA, Period 1: Placebo Period 2: SAF312 25mg b.i.d.

Change from baseline in micturition or catheterization.

Treatment sequence	Center/ Subject	Visit	Time of day	Catheterization	No. of times catheterization performed	Incontinent?	Number of times incontinence experienced
BA		P1 D1	Daytime	Yes	5	Yes	4
			Overnight	No		Yes	1
		P1 D7	Daytime	Yes	6	Yes	5
			Overnight	Yes	3	Yes	3
		P2 D1	Daytime	Yes	3	Yes	3
			Overnight	Yes	2	Yes	1
		P2 D7	Daytime	Yes	7	Yes	5
			Overnight	Yes	3	Yes	3
AB		P1 D1	Daytime	Yes	5	Yes	5
			Overnight	Yes	1	Yes	1

Sequence AB, Period 1: SAF312 25mg b.i.d. Period 2: Placebo; Sequence BA, Period 1: Placebo Period 2: SAF312 25mg b.i.d.

Safety Results

Adverse Events by System Organ Class

	SAF312 N=2 n (%)	Placebo N=1 n (%)	Total N=2 n (%)
Patients with AE(s)	2 (100.0%)	0	2 (100.0%)
Gastrointestinal disorders	1 (50.0%)	0	1 (50.0%)
General disorders and administration site conditions	1 (50.0%)	0	1 (50.0%)
Injury, poisoning and procedural complications	1 (50.0%)	0	1 (50.0%)
Investigations	1 (50.0%)	0	1 (50.0%)
Nervous system disorders	1 (50.0%)	0	1 (50.0%)
Skin and subcutaneous tissue disorders	1 (50.0%)	0	1 (50.0%)
Vascular disorders	1 (50.0%)	0	1 (50.0%)

Arranged by frequency in the total column

Most Frequently Reported AEs Overall by Preferred Term n (%)

	SAF312 N=2 n (%)	Placebo N=1 n (%)	Total N=2 n (%)
Patients with AE(s)	2 (100.0%)	0	2 (100.0%)
Blood glucose increased	1 (50.0%)	0	1 (50.0%)
Blood phosphorus decreased	1 (50.0%)	0	1 (50.0%)
Circulatory collapse	1 (50.0%)	0	1 (50.0%)
Feeling cold	1 (50.0%)	0	1 (50.0%)
Headache	1 (50.0%)	0	1 (50.0%)
Hyperhidrosis	1 (50.0%)	0	1 (50.0%)
Hypertension	1 (50.0%)	0	1 (50.0%)
Nausea	1 (50.0%)	0	1 (50.0%)
Non-cardiac chest pain	1 (50.0%)	0	1 (50.0%)
Temperature regulation disorder	1 (50.0%)	0	1 (50.0%)
Vomiting	1 (50.0%)	0	1 (50.0%)
Wound	1 (50.0%)	0	1 (50.0%)

Arranged by frequency in the total column

Serious Adverse Events and Deaths

	SAF312 N=2 n (%)	Placebo N=1 n (%)
No. (%) of subjects studied	2 (100.0%)	1 (100.0%)
No. (%) of subjects with AE(s)	2 (100.0%)	0
Number (%) of subjects with serious or other significant events		
Death	0	0
SAE(s)	1 (50.0%)	0
Discontinued due to SAE(s)	1 (50.0%)	0

Other Relevant Findings

SAF312 pharmacokinetics

Compound: SAF312 , Matrix: plasma_human , Analyte: SAF312

Treatment	Subject	Gender	Day	AUCall (Hr*ng/mL)	AUClast (Hr*ng/mL)	AUCtau (Hr*ng/mL)	Cavg (ng/mL)	Cmax (ng/mL)
SAF312 25mg b.i.d			7	575	575	575	47.9	131

Compound: SAF312 , Matrix: plasma_human , Analyte: SAF312

Treatment	Subject	Gender	Day	Cmin (ng/mL)	Fluctuation (%)	Lambda z (1/Hr)	Lambda z lower (Hr)	Lambda z upper (Hr)
SAF312 25mg b.i.d			7	18.7	234	0.114*	3.00*	12.0*

Compound: SAF312 , Matrix: plasma_human , Analyte: SAF312

Treatment	Subject	Gender	Day	T1/2 (Hr)	Tmax (Hr)	Vz F (mL)
SAF312 25mg b.i.d			7	6.08*	2.00	381000*

Date of Clinical Trial Report

19-Jul-2013

Date Inclusion on Novartis Clinical Trial Results Database

04 Sep 2013

Date of Latest Update