Full Novartis CTRD Template

Sponsor

Novartis

Generic Drug Name

TAP311

Therapeutic Area of Trial

Dyslipidemia

Approved Indication

Investigational

Protocol Number

CTAP311X2101

Title

A first-in-human randomized, double-blind, placebo-controlled, 4-part study to assess safety, tolerability, pharmacokinetics (including open label study of food effect and interaction with simvastatin) and pharmacodynamics of interwoven single- and multiple-ascending doses of TAP311 in healthy subjects and dyslipidemic patients.

Study Phase

Phase I

Study Start/End Dates

30-Nov-2011 – 15-Jun-2012

Study Design/Methodology

This was a first in human study of single and multiple escalating doses of oral TAP311. The study used an interwoven single- and multiple-ascending dose design and was divided into 4 parts (Parts I, II, III and IV). Parts I and II of the study were randomized, double-blind, placebo-controlled and conducted in a time-lagged semi-sequential manner, with Part I beginning first. Part III employed an open-label, randomized, single-dose, two-period, two-sequence, crossover design to assess TAP311 pharmacokinetic properties in healthy subjects under fasting and fed conditions. Part IV employed an open-label, multiple-dose design to assess TAP311 effect on single dose simvastatin pharmacokinetic properties in healthy subjects.

Centers

1 center in the United States

Publications

N/A

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

TAP311 1, 10, 80 mg and matching placebo capsules (administered orally once daily)

Statistical Methods

Analysis of the primary variables: In Part I and II, safety/tolerability data are listed with no formal inferential statistical analysis performed.

For Part III, AUCs and Cmax values for each analyte was logarithmically transformed and analyzed by an analysis of variance (ANOVA) with fixed effects for sequence, treatment and period, and random effect for subject. The difference (90% confidence interval (CI)) between the mean log PK parameters under non-fasting and fasting conditions were calculated and reported on the original scale for statistical inference on the ratio of geometric means.

For Part IV, AUCs and Cmax values for each analyte was logarithmically transformed and analyzed by ANOVA with fixed effect for treatment and random effect for subject. The difference (90% CI) between the mean log PK parameters in the presence and absence of TAP311 for simvastatin and simvastatin acid were calculated and reported on the original scale for statistical inference on the ratio of geometric means.

Analysis of secondary variables:

Part I:

- Percentage change from baseline in CETP activity at each time-point as well as average percentage change from baseline or time weighted average percentage change from baseline (AUC24/24) were analyzed using ANOVA with dose as the classification factor. Point estimate and the associated 95% CI for the difference between a TAP311 dose and placebo, along with the corresponding p-value were obtained.
- Cmax, Tmax, AUClast, AUC0-24, AUCinf, T1/2, Vz/F and CL/F of TAP311 following single ascending dose administration from the plasma concentration time profile.

Part II:

- HDL, LDL and apo A-I levels, in addition to CETP activity were analyzed using the same method described above for Part I data analysis.
- Cmaxss, Tmaxss, AUCtau, AUCinf, T1/2, Cavg, Fluctuation index and R accumulation (AUC) of TAP311 following multiple ascending dose administration.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Parts I, III and IV

- Healthy non-smoking males and females with no child bearing potential subjects age 18 to 65 years of age included, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
- Subjects must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 30 kg/m2.

Part II

- Dyslipidemic but otherwise healthy subjects having fasting LDL-C between 90-160 mg/dL and HDL-C ≤45 mg/dL at screening. Subjects were not treated for dyslipidemia for at least 4 weeks prior to TAP311 treatment.
- Male and female with no child bearing potential subjects 18 to 65 years of age included.
- Subjects weighing at least 50 kg with BMI within the range of 18 - 36 kg/m2.

Exclusion criteria

- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
- Active treatment for type 1 diabetes or type 2 diabetes mellitus or a fasting glucose of ≥140 mg/dL.
- A past medical history of clinically significant ECG abnormalities or clinically significant cardiovascular diseases.
- Smokers (use of tobacco products in the previous 3 months).
- Any surgical or medical condition which could have jeopardized the subject in case of participation in the study.

Participant Flow

Subject disposition - n (%) of subjects - Part I (Randomized set)

Subjects	Placebo N=14 n (%)	TAP311 1 mg N=6 n (%)	TAP311 3 mg N=6 n (%)	TAP311 10 mg N=6 n (%)	TAP311 30 mg N=6 n (%)	TAP311 100 mg N=6 n (%)	TAP311 300 mg N=6 n (%)	TAP311 600 mg N=6 n (%)	Total N=56 n (%)
Completed	14 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	56 (100)

Subject disposition - n (%) of subjects - Part II (Randomized set)

Subjects	Placebo N=10 n (%)	TAP311 3 mg N=7 n (%)	TAP311 10 mg N=7 n (%)	TAP311 30 mg N=7 n (%)	TAP311 100 mg N=7 n (%)	TAP311 160 mg N=7 n (%)	Total N=45 n (%)
Completed	10 (100%)	6 (85.7)	7 (100)	7 (100)	7 (100)	6 (85.7)	43 (95.6)
Discontinued	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	2 (4.4)
Main cause of discontinuation							
Adverse Event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (2.2)
Lost to follow-up	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)

Subject disposition - n (%) of subjects - Part III (Randomized set)

Disposition reason	Total N=18 n (%)
Completed	18 (100)

Subject disposition - n (%) of subjects - Part IV (Randomized set)

Disposition reason	Total N=18 n (%)

Disposition reason	Total N=18 n (%)
Completed	18 (100)

Baseline Characteristics

Demographic summary by treatment group - Part I (Randomized Set)

		Placebo N=14	TAP311 1 mg N=6	TAP311 3 mg N=6	TAP311 10 mg N=6	TAP311 30 mg N=6	TAP311 100 mg N=6	TAP311 300 mg N=6	TAP311 600 mg N=6	Total N=56
Age (years)	Mean (SD)	49.2 (7.94)	57.0 (6.16)	52.7 (10.61)	46.5 (10.19)	48.7 (8.85)	51.2 (7.52)	53.7 (3.44)	52.0 (6.00)	51.1 (7.96)
	Range	32, 63	47, 64	36, 62	32, 57	36, 60	44, 65	49, 59	43, 59	32, 65
Sex – n (%)	Male	6 (42.9%)		2 (33.3%)	2 (33.3%)	3 (50.0%)	2 (33.3%)		2 (33.3%)	17 (30.4%)
	Female	8 (57.1%)	6 (100.0%)	4 (66.7%)	4 (66.7%)	3 (50.0%)	4 (66.7%)	6 (100.0%)	4 (66.7%)	39 (69.6%)
Race – n (%)	Caucasian	14 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	5 (83.3%)	6 (100.0%)	5 (83.3%)	54 (96.4%)
	Black						1 (16.7%)		1 (16.7%)	2 (3.6%)
Ethnicity – n (%)	Hispanic/Latino	14 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	5 (83.3%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	55 (98.2%)
	Other	0	0	0	0	1 (16.7%)	0	0	0	1 (1.8%)
Weight (kg)	Mean(SD)	70.72 (10.241)	66.18 (5.269)	72.75 (8.353)	71.10 (9.859)	75.93 (7.207)	65.93 (5.909)	68.02 (5.219)	73.33 (14.652)	70.53 (9.059)
	Range	52.2, 87.6	60.0, 75.0	57.0, 79.1	64.0, 90.6	68.0, 86.9	58.4, 75.8	61.2, 73.9	56.0, 91.4	52.2, 91.4
Height (cm)	Mean(SD)	161.81 (10.581)	153.67 (3.077)	160.00 (7.612)	159.25 (10.059)	165.33 (11.542)	160.03 (10.205)	158.05 (3.162)	164.07 (11.446)	160.49 (9.302)
	Range	150.0, 180.7	149.0, 158.0	147.4, 166.3	148.5, 175.0	151.0, 179.4	151.0, 179.4	153.8, 162.3	147.6, 179.5	147.4, 180.7
BMI (kg/m^2)	Mean(SD)	26.918 (1.9480)	28.033 (2.1663)	28.333 (1.4969)	27.967 (1.6318)	27.849 (2.0207)	25.816 (2.1283)	27.258 (2.3530)	26.980 (2.2721)	27.326 (2.0172)
	Range	22.83, 29.96	24.97, 30.04	26.23, 30.03	25.77, 29.93	25.29, 29.82	23.39, 28.95	24.21, 29.71	23.01, 29.81	22.83, 30.04

Demographic summary by treatment group - Part II (Randomized set)

		Placebo N=10	TAP311 3 mg N=7	TAP311 10 mg N=7	TAP311 30 mg N=7	TAP311 100 mg N=7	TAP311 160 mg N=7	Total N=45
Age (years)	Mean(SD)	45.5 (7.32)	50.0 (9.07)	49.7 (5.38)	41.3 (10.31)	37.4 (8.22)	46.9 (7.97)	45.2 (8.83)
	Range	35, 56	34, 62	42, 56	25, 52	27, 49	39, 60	25, 62
Sex – n (%)	Male	6 (60.0%)	5 (71.4%)	5 (71.4%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	34 (75.6%)
	Female	4 (40.0%)	2 (28.6%)	2 (28.6%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	11 (24.4%)
Race – n (%)	Caucasian	10 (100.0%)	6 (85.7%)	7 (100.0%)	7 (100.0%)	6 (85.7%)	7 (100.0%)	43 (95.6%)
	Black		1 (14.3%)			1 (14.3%)		2 (4.4%)
Ethnicity – n (%)	Hispanic/Latino	10 (100.0%)	6 (85.7%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	6 (85.7%)	43 (95.6%)
	Other		1 (14.3%)				1 (14.3%)	2 (4.4%)
Weight (kg)	Mean(SD)	76.76 (14.877)	84.19 (10.224)	77.87 (7.508)	81.29 (10.639)	80.73 (16.787)	81.21 (13.288)	80.10 (12.313)
	Range	57.7, 103.0	70.5, 95.5	69.5, 92.2	63.2, 96.0	62.7, 107.0	58.7, 96.0	57.7, 107.0
Height (cm)	Mean(SD)	164.67 (7.512)	169.49 (9.993)	163.66 (8.671)	169.40 (6.212)	168.73 (7.742)	169.77 (9.667)	167.42 (8.247)
	Range	150.0, 177.3	156.0, 186.6	152.0, 178.0	160.0, 176.0	159.9, 180.0	151.0, 181.6	150.0, 186.6
BMI (kg/m^2)	Mean(SD)	28.081 (3.5385)	29.333 (2.9800)	29.094 (2.0779)	28.325 (3.4252)	28.110 (3.7144)	28.032 (2.8379)	28.468 (3.0347)
	Range	21.58, 32.77	24.98, 32.93	26.96, 32.81	23.27, 32.83	23.23, 33.02	25.64, 32.08	21.58, 33.02

Demographic summary by treatment group - Part III (Randomized set)

		TAP311 30 mg (Fasted)/ TAP311 30 mg (Fed) N=9	TAP311 30 mg (Fed)/ TAP311 30 mg (Fasted) N=9	Total N=18
Age (years)	Mean(SD)	44.1 (9.60)	39.2 (13.01)	41.7 (11.37)
	Range	27, 60	22, 59	22, 60
Sex - n(%)	Male	3 (33.3%)	5 (55.6%)	8 (44.4%)
	Female	6 (66.7%)	4 (44.4%)	10 (55.6%)
Race - n(%)	Caucasian	9 (100.0%)	9 (100.0%)	18 (100.0%)
Ethnicity - n(%)	Hispanic/Latino	9 (100.0%)	9 (100.0%)	18 (100.0%)
Weight (kg)	Mean(SD)	70.72 (11.986)	74.91 (8.781)	72.82 (10.418)
Height (cm)	Mean(SD)	163.88 (9.355)	165.53 (6.976)	164.71 (8.051)
	Median	161.10	163.40	163.35
BMI (kg/m^2)	Mean(SD)	26.193 (2.7164)	27.243 (1.3257)	26.718 (2.1427)
	Range	21.93, 29.38	24.24, 28.95	21.93, 29.38

Demographic summary by treatment group - Part IV

		Total N=18
Age (years)	Mean (SD)	37.6 (10.83)
	Range	21, 65
Sex - n(%)	Male	14 (77.8%)
	Female	4 (22.2%)
Race - n(%)	Caucasian	17 (94.4%)
	Black	1 (5.6%)

		Total N=18
Ethnicity - n(%)	Hispanic/Latino	18 (100.0%)
Weight (kg)	Mean (SD)	77.28 (9.800)
	Range	54.1, 89.6
Height (cm)	Mean (SD)	167.60 (9.229)
	Range	152.8, 181.7
BMI (kg/m^2)	Mean (SD)	27.424 (1.8157)
	Range	23.17, 29.59

Outcome Measures

Primary Outcome Results

Safety and tolerability were the primary outcome measured from Parts I and II of the study. **Please see Safety Section for Safety results.**

Effect of high fat food on TAP311 pharmacokinetics (Mean and SD)– Part III (PK Analysis Set)

PK Parameter	Fed (N=18)	Fasted (N=18)
Cmax (ng/mL)	566 ± 199	911 ± 197
AUClast (h*ng/mL)	51600 ± 17000	71700 ± 17500
AUCinf (h*ng/mL)	53200 ± 18000	74000 ± 19700
Tmax (h)*	12.0 (6 – 24)	6.0 (3 – 12)
T1/2 (h)	61.4 ± 13.8	62 .5 ± 13.9
Vz/F	52800 ± 13100	37400 ± 6090

*Data is presented as median (range)

Effect of TAP311 on simvastatin and simvastatin acid pharmacokinetics (Mean and SD)– Part IV (PK Analysis Set)

Analyte	PK parameter	Simvastatin alone	Simvastatin + TAP311
Simvastatin	Cmax (ng/mL)	2.2 ± 0.9	2.0 ± 1.0
	AUClast (h*ng /mL)	8.7 ± 5.5	6.9 ± 4.0
	AUCinf (h*ng/mL)[+]	9.3 ± 6.1	6.9 ± 3.0
	T1/2 (h)[a]	8.0 ± 6.6	5.2 ± 3.3
	Tmax (h)[*]	1.0 (0.5 – 3.0)	1.0 (0.5 – 6.0)
Simvastatin Acid	Cmax (ng/mL)	0.44 ± 0.2	0.72 ± 0.3
	AUClast (h*ng/mL)	4.7 ± 3.1	5.3 ± 2.5
	AUCinf (h*ng/mL)	6.0 ± 3.5	6.4 ± 2.5
	T1/2 (h)	6.1 ± 1.9	4.5 ± 1.2
	Tmax (h)[*]	4.0 (1.0 – 6.0)	4.0 (3.0 – 6.0)

Data is expressed as mean +/SD for N=18, (+ N=15, a N=17)

*Data is presented as median (range)

Secondary Outcome Results

Summary statistics (Mean and SD) of PK parameters of TAP311 following single oral doses in healthy subjects- Part I (PK Analysis Set)

Parameter	TAP311 1 mg N=5	TAP311 3 mg N=6	TAP311 10 mg N=6	TAP311 30 mg N=5	TAP311 100 mg N=6	TAP311 300 mg N=6	TAP311 600 mg N=5

Parameter	TAP311 1 mg N=5	TAP311 3 mg N=6	TAP311 10 mg N=6	TAP311 30 mg N=5	TAP311 100 mg N=6	TAP311 300 mg N=6	TAP311 600 mg N=5
AUCinf (h*ng/mL)	3750 ± 735	10200 ± 3120	27500 ± 6930	65600 ± 16700	249000 ± 51900	779000 ± 110000	1270000 ± 415000
AUC0-24 (h*ng/mL)	867 ± 110	1970 ± 374	5490 ± 1080	15400 ± 3640	61400 ± 6330	174000 ± 38100	253000 ± 77800
AUClast (h*ng/mL)	3090 ± 471	8060 ± 2080	26600 ± 6570	64200 ± 15800	243000 ± 47200	761000 ± 110000	1240000 ± 405000
Cl/F (mL/h)	274 ± 45.4	326 ± 135	393 ± 141	482 ± 124	416 ± 85.9	391 ± 53.4	514 ± 156
Cmax (ng/mL)	44.0 ± 5.60	107 ± 15.0	289 ± 55.2	825 ± 162	3890 ± 582	9710 ± 2140	14200 ± 3550
T1/2 (h)	55.3 ± 8.08	58.8 ± 11.9	65.7 ± 7.74	59.7 ± 10.1	63.2 ± 11.8	64.6 ± 10.3	62.3 ± 7.38
Tlag (h)*	1.00 (0.5 – 1.0)	1.00 (0.5 – 3.0)	0.500 (0.5 – 1.0)	0.500 (0.5 – 1.0)	0.250 (0 – 0.5)	0 (0 – 1.0)	0 (0 – 0.5)
Tmax (h)*	8.00 (6.0 – 12.0)	8.00 (6.0 – 12.0)	7.00 (4.1 – 12.1)	8.00 (4.1 – 8.0)	4.10 (3.0 – 4.1)	5.05 (3.0 – 24.1)	6.00 (4.1 – 8.0)
Vz/F (mL)	21500 ± 2080	26500 ± 7560	36300 ± 8980	40200 ± 4630	37300 ± 6810	36700 ± 9320	46300 ± 15300

*Data is presented as median (range)

Effect of single doses of TAP311 on CETP activity: Summary statistics (Mean and SD) of CETP activity in Part I (Randomized set)

Parameter	Time point	Placebo N=14	TAP311 1 mg N=6	TAP311 3 mg N=6	TAP311 10 mg N=6	TAP311 30 mg N=6	TAP311 100 mg N=6	TAP311 300 mg N=6	TAP311 600 mg N=6
CETP activity (pmol/min/mL)	**Baseline**	20.3 (4.06)	17.8 (6.42)	14.4 (3.06)	17.8 (4.00)	17.1 (5.22)	15.4 (1.99)	28.1 (5.85)	24.3 (1.84)
	Day 2 24 HOURS POST-DOSE	19.9 (4.06)	10.0 (5.11)	4.3 (1.56)	3.6 (3.23)	-1.6 (1.44)	-0.8 (2.19)	-1.9 (1.39)	3.2 (6.58)

Summary statistics (Mean and SD) of PK parameters of TAP311 following multiple oral doses in healthy subjects at Day 14- Part II (PK Analysis Set)

PK parameter	TAP311 3 mg (n=7)	TAP311 10 mg (n=7)	TAP311 30 mg (n=7)	TAP311 100 mg (n=7)	TAP311 160 mg (n=7)
AUCinf (h*ng/mL	19300 ± 4510	80800 ± 22100	180000 ± 42600	897000 ± 247000	1760000 ± 1110000
AUClast (h*ng/mL)	18600 ± 4280	78300 ± 20200	177000 ± 41500	882000 ± 244000	1710000 ± 1070000
AUC0-24 (h*ng/mL)	4670 ± 610	17700 ± 2040	48300 ± 8760	223000 ± 50200	371000 ± 179000
Cmax (ng/mL)	223 ± 32.4	887 ± 92.2	2380 ± 467	11300 ± 2560	19000 ± 9330
Cavg (ng/mL)	194 ± 25.4	739 ± 84.8	2010 ± 365	9290 ± 2090	15500 ± 7470
Tmax (h)*	6 (3-8)	4.1 (4.1-8)	6 (3-8.05)	4 (2-8.05)	4 (4-4)
T1/2 (h)	58.9 ± 10.6	64.9 ± 11.5	60.0 ± 9.60	57.8 ± 7.38	62.2 ± 12.6
Vz/F (mL)	54500 ± 7010	52600 ± 5250	55000 ± 11100	39200 ± 10400	43200 ± 14600
Cmin (ng/mL)	161 ± 28.8	581 ± 96.2	1590 ± 293	7050 ± 2290	12700 ± 6810
Fluctuation Index (%)	32.5 ± 8.41	41.9 ± 9.96	39.1 ± 7.29	46.8 ± 11.3	41.4 ± 6.01
Accumulation Ratio (AUC)	3.04 ± 0.342	3.55 ± 0.333	3.50 ± 0.284	4.77 ± 0.624	5.15 ± 1.03

*Data is presented as median (range)

Effect of TAP311 on CETP activity at steady state: Summary statistics (Mean and SD) of CETP activity in Part II (Randomized set)

Parameter	Timepoint	Placebo N=8	TAP311 3 mg N=7	TAP311 10 mg N=7	TAP311 30 mg N=7	TAP311 100 mg N=7
CETP activity (pmol/min/mL)	**Baseline**	22.2 (4.88)	22.7 (3.45)	20.7 (3.08)	21.3 (4.21)	21.9 (7.71)
	Day 14 168 HOURS POST-DOSE	22.5 (3.34)	17.8 (4.24)	11.4 (4.73)	6.3 (5.00)	-2.7 (3.02)

Effects of TAP311 on apolipoprotein A1, high density lipoprotein (HDL-C) and low density lipoprotein (LDL-C) at steady state in Part II: Summary statistics (Mean and SD) (Randomized set)

Parameter	Time point	Placebo N=10	TAP311 3 mg N=7	TAP311 10 mg N=7	TAP311 30 mg N=7	TAP311 100 mg N=7	TAP311 160 mg N=6
Apolipoprotein A1	Baseline	121.6 (11.43)	135.5 (9.53)	125.4 (14.68)	122.5 (13.42)	119.4 (12.54)	122.5 (10.55)
(mg/dL)	Day 14	117.3 (13.66)	146.6 (16.21)	167.9 (12.40)	175.9 (15.90)	156.9 (29.34)	159.0 (22.24)
HDL-C	Baseline	38.6 (5.21)	41.0 (4.04)	35.0 (6.23)	36.8 (3.82)	37.7 (7.27)	37.2 (5.03)
(mg/dL)	Day 14	38.3 (8.51)	60.7 (7.20)	88.6 (7.76)	98.1 (13.79)	87.6 (26.95)	80.5 (15.91)
LDL-C	Baseline	133.1 (33.14)	126.1 (13.35)	126.0 (17.90)	111.9 (15.89)	124.2 (31.11)	149.3 (23.22)
(mg/dL)	Day 14	131.6 (31.04)	97.6 (17.79)	72.1 (17.07)	56.1 (9.34)	63.4 (23.40)	63.5 (8.64)

Safety Results

Adverse Events by System Organ Class

Incidence of AEs by system organ class - n (%) of subjects (All subjects) - Part I (Safety Set)

Body System	Placebo N=14 N (%)	TAP311 1 mg N=6 N (%)	TAP311 3 mg N=6 N (%)	TAP311 10 mg N=6 N (%)	TAP311 30 mg N=6 N (%)	TAP311 100 mg N=6 N (%)	TAP311 300 mg N=6 N (%)	TAP311 600 mg N=6 N (%)	Total N=56 N (%)
Any Body System	2 (14.3)	3 (50.0)	2 (33.3)	3 (50.0)	2 (33.3)	1 (16.7)	2 (33.3)	4 (66.7)	19 (33.3)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (1.8)
Eye Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)
Gastrointestinal Disorders	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	3 (50.0)	6 (10.7)
General Disorders and Administration Site Conditions	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	3 (5.4)
Infections and Infestations	1 (7.1)	0 (0.0)	0 (0.0)	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.1)
Investigations	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Musculoskeletal and Connective Tissue Disorders	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Nervous System Disorders	0 (0.0)	2 (33.3)	2 (33.3)	0 (0.0)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	9 (16.1)

Body System	Placebo N=14 N (%)	TAP311 1 mg N=6 N (%)	TAP311 3 mg N=6 N (%)	TAP311 10 mg N=6 N (%)	TAP311 30 mg N=6 N (%)	TAP311 100 mg N=6 N (%)	TAP311 300 mg N=6 N (%)	TAP311 600 mg N=6 N (%)	Total N=56 N (%)
Reproductive System and Breast Disorders	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Respiratory, Thoracic and Mediastinal Disoders	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)

Incidence of AEs by system organ class - n (%) of subjects (All subjects) - Part II (Safety Set)

Body System	Placebo N=10	TAP311 3 mg N=7	TAP311 10 mg N=7	TAP311 30 mg N=7	TAP311 100 mg N=7	TAP311 160 mg N=7	Total N=45
Any Body System	6 (60.0)	4 (57.1)	1 (14.3)	1 (14.3)	6 (85.7)	2 (28.6)	20 (44.4)
Blood and Lymphatic System Disorders	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Gastrointestinal Disorders	5 (50.0)	3 (42.9)	0 (0.0)	0 (0.0)	5 (71.4)	2 (28.6)	15 (33.3)
Infections and Infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (10.0)	2 (4.4)
Investigations	1 (10.0)	2 (28.6)	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	5 (11.1)
Metabolism and Nutrition Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	2 (4.4)
Nervous System Disorders	2 (20.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.7)
Renal and Urinary Disorders	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	2 (4.4)
Respiratory, Thoracic and Mediastinal Disoders	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Skin and Subcutaneous Tissue Disorders	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)

No AE's reported in Part III.

Incidence of AEs by system organ class - n (%) of subjects (All subjects) - Part IV (Safety Set)

	Total N=18
Any body system	2 (11.1%)
Gastrointestinal Disorders	1 (5.6%)
Investigations	1 (5.6%)

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

Incidence of AEs by preferred term - n (%) of subjects (All subjects) - Part I (Safety Set)

	Placebo N=14	TAP311 1 mg N=6	TAP311 3 mg N=6	TAP311 10 mg N=6	TAP311 30 mg N=6	TAP311 100 mg N=6	TAP311 300 mg N=6	TAP311 600 mg N=6	Total N=56
Subjects with AE(s)	2 (14.3%)	3 (50.0%)	2 (33.3%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	4 (66.7%)	19 (33.9%)
Headache	0 (0.0%)	2 (33.3%)	2 (33.3%)	0 (0.0%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	9 (16.1%)
Nausea	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	3 (5.4%)
Vomiting	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	3 (5.4%)

	Placebo N=14	TAP311 1 mg N=6	TAP311 3 mg N=6	TAP311 10 mg N=6	TAP311 30 mg N=6	TAP311 100 mg N=6	TAP311 300 mg N=6	TAP311 600 mg N=6	Total N=56
Diarrhea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (16.7%)	2 (3.6%)
Fatigue	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	2 (3.6%)
Viral upper respiratory tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
Abdominal pain upper	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (1.8%)
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (1.8%)
Blood creatine phosphokinase increase	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Conjunctival hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Folliculitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Influenza like illness	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Muscle spasms	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Nasal congestion	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Ocular hyperaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Otitis externa	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Vulvovaginal pruritus	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)

Arranged by frequency in total group

Incidence of AEs by preferred term - n (%) of subjects (All subjects) - Part II (Safety Set)

	Placebo N=10	TAP311 3 mg N=7	TAP311 10 mg N=7	TAP311 30 mg N=7	TAP311 100 mg N=7	TAP311 160 mg N=7	Total N=45
Subjects with AE(s)	6 (60.0%)	4 (57.1%)	1 (14.3%)	1 (14.3%)	6 (85.7%)	2 (28.6%)	20 (44.4%)
Constipation	3 (30.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	3 (42.9%)	2 (28.6%)	9 (20.0%)
Abdominal distension	2 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (57.1%)	1 (14.3%)	7 (15.6%)
Headache	2 (20.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.7%)
Decreased appetite	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	2 (4.4%)
Pancreatic enzymes increased	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	2 (4.4%)
Anaemia	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Blood alkaline phosphotase increased	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Blood creatine phosphokinase increase	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Dyspepsia	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Dysuria	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Flatulence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (2.2%)
Frequent bowel movements	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (2.2%)
Gastritis	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Liver function test abnormal	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)

	Placebo N=10	TAP311 3 mg N=7	TAP311 10 mg N=7	TAP311 30 mg N=7	TAP311 100 mg N=7	TAP311 160 mg N=7	Total N=45
Nasal congestion	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Nausea	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Occult blood positive	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Oral herpes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (2.2%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (2.2%)
Urinary hesitation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (2.2%)
Viral upper respiratory tract infection	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)

Arranged by frequency in total group

No AEs were reported in Part III of the study.

Incidence of AEs by preferred term - n (%) of subjects (All subjects) - Part IV

	Total N=18
Subjects with AE(s)	2 (11.1%)
Flatulence	1 (5.6%)
Pancreatic enzymes increased	1 (5.6%)

Serious Adverse Events and Deaths

No deaths or serious adverse events reported in this study.

Other Relevant Findings

N/A

Date of Clinical Trial Report

8 MAY 2013

Date Inclusion on Novartis Clinical Trial Results Database

12 JUN 2013

Date of Latest Update

05 JUN 2013