Sponsor

Novartis

Generic Drug Name

APL180

Therapeutic Area of Trial

Coronary artery disease

Approved Indication

Investigational

Study Number

CAPL180A2201

Title

A first-in-human, randomized, double-blind, placebo-controlled, single-ascending dose (healthy volunteers and coronary heart disease (CHD) patients) and multiple dose (CHD patients) study to assess safety, tolerability, pharmacokinetics (PK)and pharmacodynamics (PD) of APL180

Phase of Development

II

Study Start/End Dates

24-Sep-2007 to 17-Aug-2009

Study Design/Methodology

This was a three part, randomized, double-blinded, placebo-controlled, multicenter, single- and multiple ascending dose study to assess safety, tolerability, PK and PD of APL180 in healthy subjects and CHD patients or a those with a CHD equivalent. In Parts I and II, subjects/patients received a intravenous (IV) single dose while in Part III, the patients received seven IV daily infusions of APL180 or placebo according to the randomization schedule.

Centres

The study was conducted at a total of 10 centers at Netherlands (1), Israel (3), South Africa (2), Denmark (1), Belgium (1), Great Britain (1) and United States of America (1).

Publication

Not yet published.

Objectives

Primary objective(s)

- To determine the safety and tolerability of APL180 after single i.v infusion in healthy subjects and CHD patients and after 7 daily i.v. infusions in CHD patientsTo determine the pharmacokinetics of APL180 after single i.v infusion in healthy subjects and CHD patients and after 7 daily i.v. infusions in CHD patients
- To evaluate effects of APL180 on biomarkers of HDL function after single i.v. infusion and 7 daily i.v. infusions in CHD patients

Secondary objective(s)

- To explore the PK/PD relationship after a single i.v. infusion and 7 daily i.v. infusions in CHD patients

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

APL180 was supplied as lyophilized powder in a sterile vial. It was administered as a single dose of 0.3, 1, 3 & 10 mg to healthy subjects, and 1, 3, 10, 30, 60 and 100 mg to CHD patients and as 7 daily doses of 3, 10, 30 and 100 to CHD patients. These doses were administered as a two hour (hr) IV infusion.

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

Placebo was supplied as lyophilized powder in a sterile vial and administered as a two hour (hr) IV infusion.

Criteria for Evaluation

Primary variables

- Safety: Standard clinical laboratory evaluations (hematology, blood chemistry, urine analysis), vital signs measurements, ECG evaluations, adverse events (AEs) and serious adverse events (SAEs).
- Pharmacokinetics: The following PK parameters AUClast, AUCinf, Cmax, Tmax, and T1/2 were determined using non-compartmental method. Biofluid concentrations were expressed in mass per volume units. Pharmacokinetic parameters were determined using non-compartmental method(s) using WinNonlin Pro (Version 5.2).
- Pharmacodynamic / Biomarkers: Assessment of core biomarkers included the cell-based assay (CBA), cell-free assay (CFA), paraoxonase (PON) activity, pre-β migrating HDL (pre-β HDL), high-sensitivity CRP (hsCRP) and interleukin-6 (IL-6).

Secondary variables

- Pharmacokinetics: The following PK parameters AUClast, AUCinf, Cmax, Tmax, and T1/2 were determined using non-compartmental method. Biofluid concentrations were expressed in mass per volume units. PK parameters were determined using non-compartmental method(s) using WinNonlin Pro (Version 5.2).
- Pharmacodynamic / Biomarkers: Assessment of core biomarkers included the cell-based assay (CBA), cell-free assay (CFA), paraoxonase (PON) activity, pre-β migrating HDL (pre-β HDL), high sensitivity CRP (hsCRP) and interleukin-6 (IL-6).

Safety and tolerability

Standard clinical laboratory evaluations (hematology, blood chemistry, urine analysis), vital signs measurements, ECG evaluations, AEs and SAEs.

Pharmacology

Not applicable.

Other

Exploratory biomarkers included 1) lipoprotein profile: HDL-C and LDL-C and subpopulations, ApoAI and ApoAII, total cholesterol (TC), IDL-C, VLDL-C and Non-HDL-c; 2) Oxidation status: OxLDL (via Mercodia's assay), OxPL on ApoAI and ApoB containing lipoproteins (via EO6 Ab), were determined.

Statistical Methods

PK, PD, and biomarker data from Part I, II and Part III were listed and analyzed separately. An analysis of covariance (ANCOVA) with classification by treatment and baseline as the covariate was performed on change from baseline at each time point. The null hypothesis H0: $\Delta = 0$ versus the alternative hypothesis HA: $\Delta \neq 0$, where Δ denotes the mean difference between APL180 and placebo treatment groups, was tested at the 5% significance level. Additionally, the day seven average change from baseline was analyzed using the same approach described above. With the exception of CBA data, all biomarker data were log-transformed prior to statistical analysis. Dose escalation decision was mainly based on blinded clinical review of the safety and tolerability data for each dose cohort. At the completion of Part I of the study, the PK data were analyzed to guide dose selection in Part II of the study. After each cohort of Part II of the study had completed treatment, the PK data and the key PD biomarker data were analyzed to provide guidance on the subsequent dose cohorts and subsequent formulation development. The safety, PK data and key PD biomarker data from all ascending dose cohorts of Part II and the safety data from Part III were analyzed to guide dose selection for cohort MD1 of Part III of the study.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria for Part I (healthy volunteers) only

1. Male and female subjects age 18 to 55 years of age included, in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening and baseline
2. Female subjects must be of non-childbearing potential. They must have been surgically sterilized at least 6 months prior to screening or be postmenopausal. Surgical sterilization procedures must be supported with clinical documentation made available to sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the eCRFs. Postmenopausal women must have no regular menstrual bleeding for at least 2 years prior to inclusion. Menopause will be confirmed by a plasma FSH level of >40 IU/L.
3. Body mass index (BMI) must be within the range of 18 to 30 kg/m^2, inclusive
4. Vital signs should be within the following ranges at screening and baseline:

   oral body temperature between 35.0-37.5 °C
   supine systolic blood pressure, 85-140 mm Hg
   supine diastolic blood pressure, 50-90 mm Hg
   supine pulse rate, 40 - 90 bpm

   After 3 minutes standing, there shall be no more than a 20 mm Hg drop in systolic or 10 mm Hg drop in diastolic blood pressure and increase in heart rate (>20 bpm) associated with clinical manifestation of postural hypotension
5. Male subjects, when sexually active, must use of one form of highly effective contraception (e.g. condom) for the duration of the study and for a 3 months periods after the last dose. Specifically, if the female partner of this male trial subject is pregnant, a condom must be used in order to prevent exposure to the fetus through semen. Effective contraception procedures must be supported with clinical documentation made available to sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the eCRFs.

6. Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent.

Inclusion criteria for Parts II and III (CHD patients) only:

1. Male and female CHD or CHD equivalents patients (as defined by the NCEP ATPIII criteria given below:
   - **Clinical CHD patients**
     - MI, angina, revascularization (e.g. CABG, stent) at least 6 months prior to inclusion
   - **CHD equivalent patients**
     - symptomatic carotid artery disease (e.g. transient ischemic attack or stroke of carotid origin)
     - peripheral artery disease
     - abdominal aortic aneurysm
     - Diabetes Mellitus (HbA1c ≤9)
     - 20% 10 year risk of CHD (Framingham point score: ≥16 (men), ≥23 (women))
   - **Patients with other clinical forms of atherosclerotic disease including:**
     - >50 percent stenosis on angiography or ultrasound
     - other forms of clinical atherosclerotic disease (e.g. renal artery disease)
2. Female subjects must be of non-childbearing potential. They must have been surgically sterilized at least 6 months prior to screening or be postmenopausal. Surgical sterilization procedures must be supported with clinical documentation made available to sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the eCRFs. Postmenopausal women must have no regular menstrual bleeding for at least 2 years prior to inclusion. Menopause will be confirmed by a plasma FSH level of >40 IU/L.
3. Patients must be 18 to 75 years of age, inclusive
4. Body mass index (BMI) must be within the range of 20 to 38 kg/m^2, inclusive
5. Patients must have a hsCRP at screening or baseline between 2-20 mg/L (This hsCRP criteria pertained to Part II only.
6. Patient must have been on a stable statin therapy for >8 weeks prior to first dose
7. Patients must be willing maintain all current chronic medications without change in frequency or duration from first dose until Study completion
8. Male subjects, when sexually active, must use of one form of highly effective contraception (e.g. condom) for the duration of the study and for a 3 months periods after the last dose. Specifically, if the female partner of this male trial subject is pregnant, a condom must be used in order to prevent exposure to the fetus through semen. Effective contraception procedures must be supported with clinical documentation made available to sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the eCRFs.
9. Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent.

Exclusion criteria

Subjects meeting any of the following criteria will be excluded from entry into or continuation in the study unless sponsor approval is obtained.

Exclusion criteria for Parts I-III (healthy volunteers and CHD patients)

1. Pregnancy
2. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations.
3. Donation or loss of 400 ml or more of blood within 8 weeks prior to first dosing, or longer if required by local regulation.
4. Significant illness within two weeks prior to dosing.
5. Active or recent bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated),
6. A known hypersensitivity to the study drug or drugs similar to the study drug or any allergic reaction to prior receipt of protein therapies or vaccines.
7. History of poor vein access
8. Active gallbladder disease
9. Serum creatine kinase CK (CPK) total > 2x ULN
10. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result
11. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result
12. History of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations. Positive drug screen during the study is also exclusionary.
13. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
14. Any condition that in the opinion of the investigator or the Novartis medical monitor would jeopardize the evaluation of efficacy or safety. For example, evidence of renal or hepatic disease.

    SGPT, SGOT and direct bilirubin will have to be strictly within the normal range before inclusion, GGT and alkaline phosphatase must not exceed twice the upper limit of the normal range.

    If the total bilirubin concentration is increased above 1.5 times the upper normal limit total bilirubin should be differentiated into the direct and indirect reacting bilirubin
15. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
16. Fasting triglycerides ≥ 500 mg/dl (5.65 mmol/l).

Exclusion criteria for Part I (healthy volunteers) only

1. Smokers (use of tobacco products in the previous 3 months). Urine cotinine levels will be measured during screening for all subjects. Smokers will be defined as any subject who reports tobacco use or has a urine cotinine greater than 500 ng/ml
2. Use of any prescription drugs within four (4) weeks prior dosing, or over-the-counter (OTC) medication (vitamins, herbal supplements, dietary supplements) within two (2) weeks prior to dosing. Paracetamol is acceptable, but must be documented in the concomitant medications / significant non-drug therapies page of the CRF.
3. A past medical history of clinically significant ECG abnormalities or a family history grandparents, parents and siblings) of a prolonged QT-interval syndrome.
4. Clinical evidence of any abnormal laboratory value which might significantly jeopardize the subject in case of participation in the study. If the lab values are within 10% of normal range and are not deemed clinically significant by senior clinical staff in the clinical unit and the subject is otherwise in healthy condition, the subject can be included in the study.

Exclusion criteria for Parts II and III (CHD patients) only

1. Smokers who report cigarette use of more than 10 cigarettes per day. Urine cotinine levels will be measured during screening. Smokers will be defined as any subject who reports cigarette use or has a urine cotinine greater than 500 ng/mL. As smoking could effect HDL function and thus confound biomarker readings, smokers will not be allowed to smoke for 10 hours prior to dosing until 24 hours post-dose on any day when PD samples are collected.
2. Presence of NYHA Class III or IV chronic heart failure or unstable angina pectoris
3. MI or angioplasty (including stenting), acute coronary syndrome (ACS), unstable angina or arterial embolic disease within 6 months prior to dosing
4. CHD equivalent patients (as defined above) with an early positive exercise stress test (i.e. diagnostic ischemic ST changes within first 3 minutes of exercise)
5. Troponin I levels > 1 x ULN
6. Use of niacin >500 mg/day, within 6 weeks
7. Use of fibrates, within the past 6 weeks
8. Uncontrolled diabetes (HbA1c > 9, FPG > 12 mmol/l, hypoglycemic event in last 3 months)
9. Use of insulin or GLP-1 analogs within last 3 months or change in oral anti-diabetic medication within last 3 months.
10. Use of warfarin, or any known coagulopathy and /or elevated PT/PTT >1.5 x ULN
11. Use of any anti-inflammatory medicine (ibuprofen etc.) within two (2) weeks prior to dosing, except chronic aspirin. Paracetamol is acceptable, but must be documented in the Concomitant medications / significant non-drug therapies page of the CRF.
12. Uncontrolled hypertension (Systolic BP >160 mm Hg and/or Diastolic BP >100 mmHg on two consecutive measurements)

Number of Subjects

	Novartis product	Comparator
Planned N	128	48
Randomised n	128	48
Intent-to-treat population (ITT) n (%)	128	48
Completed n (%)	128 (100)	46 (97)
Withdrawn n (%)	0 (0)	2 (3)
Withdrawn due to adverse events n (%)	0 (0)	0 (0)
Withdrawn due to lack of efficacy n (%)	0 (0)	0 (0)
Withdrawn for other reasons n (%)	0 (0)	2 (3)

Demographic and Background Characteristics

Part I:

Demographic variables	SD-HV APL 180 0.3 mg N=6	SD-HV APL 180 1 mg N=6	SD-HV APL 180 3 mg N=6	SD-HV APL 180 10 mg N=6	SD-HV Placebo N=8	SD-HV All subjects N=32
Age (years)						
n	6	6	6	6	8	32
mean	40.3	29.3	24.7	27.0	35.0	31.5
SD	16.31	14.99	3.44	8.65	12.80	12.74
Height (cm)						
n	6	6	6	6	8	32
mean	175.00	183.67	181.67	179.33	177.63	179.34
SD	10.640	6.743	5.574	5.820	8.245	7.778
Weight (kg)						
n	6	6	6	6	8	32
mean	74.45	72.07	82.70	77.78	79.08	77.33
SD	9.673	7.726	12.501	5.339	10.347	9.596
Sex						
Male	4 (66.7%)	6 (100%)	6 (100%)	6 (100%)	8 (100%)	30 (93.8%)
Female	2 (33.3%)	0	0	0	0	2 (6.3%)
Race						
Caucasian	5 (83.3%)	6 (100%)	4 (66.7%)	5 (83.3%)	7 (87.5%)	27 (84.4%)
Black	1 (16.7%)	0	2 (33.3%)	0	0	3 (9.4%)
Asian	0	0	0	0	1 (12.5%)	1 (3.1%)
Other	0	0	0	1 (16.7%)	0	1 (3.1%)
Ethnicity						
Hispanic/Latino	0	0	1 (16.7%)	0	0	1 (3.1%)
Other	6 (100%)	6 (100%)	5 (83.3%)	6 (100%)	8 (100%)	31 (96.9%)
BMI (kg/m2)						
n	6	6	6	6	8	32
mean	24.31	21.45	25.00	24.23	25.09	24.08
SD	2.414	3.000	3.101	2.012	2.897	2.875

Part II:

Demographic variables	SD-CHD APL 180 1 mg N=10	SD-CHD APL 180 3 mg N=10	SD-CHD APL 180 10 mg N=10	SD-CHD APL 180 30 mg N=10	SD-CHD APL 180 60 mg N=10	SD-CHD APL 180 100 mg N=10	SD-CHD Placebo N=12	SD-CHD All subjects N=72
Age (years)								
n	10	10	10	10	10	10	12	72
mean	63.3	63.2	56.5	60.4	61.7	54.8	63.3	60.5
SD	9.17	4.92	9.18	7.31	8.27	8.57	5.97	8.08
Height (cm)								
n	10	10	10	10	10	10	12	72
mean	167.50	164.70	172.10	172.90	176.40	171.90	172.08	171.11
SD	7.531	10.296	7.400	8.517	6.059	4.483	11.587	8.785
Weight (kg)								
n	10	10	10	10	10	10	12	72
mean	83.13	80.43	91.83	80.55	96.90	86.42	88.61	86.89
SD	13.240	13.346	9.940	16.273	10.698	13.586	13.587	13.748
Sex								
Male	6 (60.0%)	6 (60.0%)	6 (60.0%)	7 (70.0%)	10 (100%)	9 (90.0%)	9 (75.0%)	53 (73.6%)
Female	4 (40.0%)	4 (40.0%)	4 (40.0%)	3 (30.0%)	0	1 (10.0%)	3 (25.0%)	19 (26.4%)
Race								
Caucasian	10 (100%)	4 (40.0%)	7 (70.0%)	9 (90.0%)	10 (100%)	9 (90.0%)	12 (100%)	61 (84.7%)
Black	0	3 (30.0%)	3 (30.0%)	1 (10.0%)	0	0	0	7 (9.7%)
Asian	0	2 (20.0%)	0	0	0	0	0	2 (2.8%)
Other	0	1 (10.0%)	0	0	0	1 (10.0%)	0	2 (2.8%)
Ethnicity								
Hispanic/Latino	0	0	0	3 (30.0%)	6 (60.0%)	3 (30.0%)	2 (16.7%)	14 (19.4%)

Mixed ethnicity	0	1 (10.0%)	0	0	0	1 (10.0%)	0	2 (2.8%)
Other	10 (100%)	9 (90.0%)	10 (100%)	7 (70.0%)	4 (40.0%)	6 (60.0%)	10 (83.3%)	56 (77.8%)
BMI (kg/m2)								
n	10	10	10	10	10	10	12	72
mean	29.56	29.63	30.94	26.82	31.15	29.22	29.80	29.59
SD	3.962	3.936	1.877	4.460	3.189	4.221	2.719	3.650

Part III:

Demographic subjects variables	MD-CHD APL 180 3 mg N=6	MD-CHD APL 180 10 mg N=6	MD-CHD APL 180 30 mg N=26	MD-CHD APL 180 100 mg N=6	MD-CHD Placebo N=28	MD-CHD All N=72
Age (years)						
n	6	6	26	6	28	72
mean	55.8	60.0	59.7	64.2	60.7	60.2
SD	6.49	4.65	7.47	4.71	7.57	7.11
Height (cm)						
n	6	6	26	6	28	72
mean	173.33	173.83	171.54	171.83	172.21	172.17
SD	11.553	4.119	9.318	8.232	9.681	9.060
Weight (kg)						
n	6	6	26	6	28	72
mean	88.97	90.17	87.52	81.62	89.10	87.98
SD	10.191	10.926	14.724	20.786	17.896	15.772
Sex						
Male	4 (66.7%)	4 (66.7%)	19 (73.1%)	6 (100%)	19 (67.9%)	52 (72.2%)
Female	2 (33.3%)	2 (33.3%)	7 (26.9%)	0	9 (32.1%)	20 (27.8%)
Race						
Caucasian	5 (83.3%)	6 (100%)	21 (80.8%)	5 (83.3%)	22 (78.6%)	59 (81.9%)
Black	1 (16.7%)	0	3 (11.5%)	0	5 (17.9%)	9 (12.5%)
Asian	0	0	0	1 (16.7%)	0	1 (1.4%)
Other	0	0	2 (7.7%)	0	1 (3.6%)	3 (4.2%)
Ethnicity						
Indian(Indian subcontinent)	0	0	0	1 (16.7%)	0	1 (1.4%)
Other	6 (100%)	6 (100%)	26 (100%)	5 (83.3%)	28 (100%)	71 (98.6%)
BMI (kg/m2)						
n	6	6	26	6	28	72
mean	29.64	29.96	29.63	27.30	29.82	29.54
SD	2.485	4.441	3.567	4.525	3.870	3.731

Primary Objective Result(s)

Part I: Summary of Pharmacokinetic parameters of APL180 in healthy volunteers following IV infusion (0.3-10mg)

PK Parameters	Dose: 0.3 mg (N = 6)	Dose: 1 mg (N = 6)	Dose: 3 mg[1] (N = 5)	Dose: 10 mg (N = 6)
Cmax (ng/mL)	40.9±14.8	106.8±10.5	377.8±107.3	1170±117.6
AUC0-tlast (ng*h/mL)	117.2±47.8	299.4±38.1	1258.7±544.4	3565±265.6
AUCinf (ng*hr/mL)	124.8±49.7	307.2±37.3	1265±547.2	3573.5±266.2
Tmax (h)*	2.25[2.0 – 2.3]	0.26[0.26 – 2.0]	2.0[0.25 – 2.0]	1.5[0.25 – 2.0]
T1/2(h)	1.0 ± 0.24	0.8±0.2	1.1±0.4	1.1±0.2
Cl (L/h)	2.76±1.1	3.29±.38	2.65±0.83	2.81±0.21

Data represent mean ± standard deviation
1. Data from subject 0001_34102 was excluded (Cmax: 17.5 ng/mL, AUCinf: 150.8 ng*h/mL, and Tmax: 4.0 hrs) *median[rang] was presented;

Part II: **Summary of PK parameters of APL180 in CHD patients following IV infusion (1-100 mg)**

PK Parameters	1 mg (N=10)	3 mg (N=10)	10 mg (N=10)	30 mg (N=10)	60 mg[1] (N=9)	100 mg (N=10)
Cmax (ng/mL)	155.6±75.4	415.4±102.9	1322.8±321.7	3774±962	6575.6±1451	12161±3534.2
AUC0-tlast (ng*h/mL)	443.3±116.5	1312±413.5	4253.6±1352	11266.9±3179	21051±6030	37353±13071
AUCinf (ng*hr/mL)	450.6±116	1322.2±417.3	4262.5±1352	11278.8±3181	21066±6040	37376±13086
Tmax (h)*	1.0[0.25 – 2.3]	1.5[0.25 – 2.0]	1.0[0.25 – 2.0]	0.28[0.25 – 2.4]	2.0[0.25-2.0]	0.65 [0.25 – 2.0]
T1/2(h)	1.05±0.2	1.1±0.24	1.5±0.4	1.2±0.3	1.4±0.3	1.2±0.2
Cl(L/h)	2.37±0.67	2.54±1.0	2.53±0.69	2.88±0.89	3.08±0.99	2.94±0.88

Data represent mean ± standard deviation
1. Data from subject 0082_18105 was excluded (Cmax:558 ng/mL, AUCinf: 2891.8 ng*h/mL and Tmax: 3.0 hrs; *median[rang] was presented.

Part III:

Summary of PK parameters of APL180 in CHD patients following multiple dose infusion (3-100 mg)

PK Parameters	3 mg (N=6)		10 mg (N=6)		30 mg (N=26)		100 mg (N=6)	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Cmax (ng/mL)	319±42	323.8±51	1067.8 ±117.8	1000.3 ±143	3254.6 ±640.2	2906.7 ±797.4	10773 ±4877	10062 ±3190
AUCtau# (ng*hr/mL)	1086.9 ±110.6	1099.8 ±145.1	3559.7 ±590.4	3416.3 ±505.1	10852.7 ±2565.6	9584.8 ±3094.7	36114 ±16924	33700 ±10227
Tmax* (h)	1.0 [0.25-1.0]	1.5 [0.25-2.0]	1.5 [0.25 – 2.25]	1.0 [0.25 – 2.0]	1.5 [0.25 – 2.0]	1.63 [0.25 – 2.0]	1.5 [1.0 – 2.0]	2.0 [0.25 – 2.0]
T1/2(h)	1.25 ±0.22	1.46 ±0.33	1.65 ±0.5	1.5 ±0.5	1.43 ±0.3	1.47 ±0.4	1.6 ±0.5	1.6 ±0.5
Cl (L/h)	2.78 ±0.29	2.76 ±0.34	2.87 ±0.42	2.97 ±0.38	2.93 ±0.8	3.49 ±1.33	3.36 ±1.67	3.16 ±0.8
Cavg (ng/mL)		45.8±6.0		142.4 ±21		399.3 ±129		1404.1 ±426
Accumulati	1.01 ± 0.1		0.96 ± 0.05		0.88±0.18		1.1±0.45	

Minimum-Maximum	112 – 226	130-235	112-235
Week 6 [1]			
N	781	771	1552
Mean ± SD	146.8 ± 18.24	140.2 ± 17.58	143.5 ± 18.22
Median	145.0	138.0	142.0
Minimum-Maximum	95-215	95-208	95-215

Summary of statistically significant results from analysis of core biomarkers at each time point in Part II:

	Hour	Dose (mg)	N	Ratio of geometric means (post-dose/baseline) vs. placebo*	95% CI	p-value
CBA	4	100	10	0.23	0.02, 0.44	0.031
CFA	.25	1	9	0.74	0.59, 0.92	0.009
	4	3	10	0.76	0.58, 0.99	0.040
	12	60	10	1.66	1.21, 2.27	0.002
	24	30	9	1.28	1.01, 1.62	0.043
PON	2	30	10	0.90	0.82, 0.99	0.029
	4	30	10	0.84	0.76, 0.93	0.001
	24	30	10	0.84	0.75, 0.95	0.006
Pre-Beta	4	100	10	0.73	0.54, 0.98	0.037
	12	100	10	0.70	0.51, 0.96	0.027
	24	3	10	0.74	0.60, 0.96	0.021
hsCRP	2	100	10	1.25	1.02, 1.54	0.033
	8	100	10	1.30	1.01, 1.68	0.040
	12	100	10	1.37	1.05, 1.80	0.023

*For CBA, difference between treatments in change from baseline is presented. Source:

Summary of results from statistical analysis of core biomarker average and trough values comparing APL180 30 mg and placebo treatments in Part III:

		N#	Ratio of geometric means (post-dose/baseline) vs. placebo*	95% CI	p-value
CBA	Day 1 Average	26/27	-0.05	-0.13, 0.03	0.249
	Day 7 Pre-Dose	26/25	-0.10	-0.16, -0.04	0.003
	Day 7 24H Post-Dose	26/25	-0.13	-0.19, -0.06	0.000
	Day 7 Average	26/25	-0.12	-0.23, -0.01	0.029
CFA	Day 1 Average	24/25	0.98	0.88, 1.10	0.78
	Day 7 Pre-Dose	23/20	0.84	0.66, 1.07	0.151
	Day 7 24H Post-Dose	22/21	0.87	0.69, 1.08	0.205
	Day 7 Average	24/23	0.90	0.74, 1.09	0.279
PON	Day 1 Average	26/27	1.04	0.99, 1.08	0.092
	Day 7 Pre-Dose	26/25	1.01	0.93, 1.09	0.845
	Day 7 24H Post-Dose	26/25	1.08	1.01, 1.15	0.027
	Day 7 Average	26/25	1.05	0.99, 1.11	0.123
Pre-Beta	Day 1 Average	26/28	1.00	0.91, 1.09	0.936
	Day 7 Pre-Dose	26/26	0.92	0.80, 1.07	0.286
	Day 7 24H Post-Dose	26/26	0.81	0.63, 1.03	0.085
	Day 7 Average	26/26	0.85	0.73, 0.99	0.035
hsCRP	Day 1 Average	26/27	1.02	0.95, 1.09	0.557
	Day 7 Pre-Dose	26/25	1.49	1.07, 2.08	0.020
	Day 7 24H Post-Dose	25/25	1.51	1.02, 2.22	0.038
	Day 7 Average	26/25	1.51	1.09, 2.09	0.014
IL6	Day 1 Average	26/27	1.02	0.84, 1.24	0.823
	Day 7 Pre-Dose	26/25	1.21	0.94, 1.57	0.140
	Day 7 24H Post-Dose	25/25	1.09	0.76, 1.56	0.640
	Day 7 Average	26/25	1.19	0.92, 1.55	0.186

N for APL180 30 mg/ N for Placebo.
* For CBA, difference between treatments in change from baseline is presented.

Safety results: see under Safety.

Secondary Objective Result(s)

Despite achieving targeted exposures (Cmax > 10,000 ng/mL an AUC > 33,000 ng*h/mL), no improvements in biomarkers of HDL function (CBA, CFA, PON or pre-í HDL) were observed. In addition, there was no trend for improvement in CBA with increasing exposure noted.

A trend towards increases in inflammatory markers (IL-6 and hsCRP) upon treatment with APL180 was observed. For hsCRP, a ~50% increase in the geometric mean was observed on Day 7 at all dose levels of APL180 though no exposure/response was noted. For IL-6, no dose-response was noted, while there appeared to be a slight increase in response with exposure levels.

Safety Results

Part II:

Body system Preferred Term	SD-CHD APL180 1 mg (N=10)	SD-CHD APL180 3 mg (N=10)	SD-CHD APL180 10 mg (N=10)	SD-CHD APL180 30 mg (N=10)	SD-CHD APL180 60 mg (N=10)	SD-CHD APL180 100 mg (N=10)	SD-CHD All APL180 subjects (N=60)	SD-CHD Placebo (N=12)
-Any Body System								
-TOTAL	2 (20.0)	5 (50.0)	9 (90.0)	4 (40.0)	7 (70.0)	6 (60.0)	33 (55.0)	6 (50.0)
Cardiac disorders								
-TOTAL	0	0	0	0	1 (10.0)	0	1 (1.7)	1 (8.3)
Palpitations	0	0	0	0	0	0	0	1 (8.3)
Tachycardia	0	0	0	0	1 (10.0)	0	1 (1.7)	0
Gastrointestinal disorders								
-TOTAL	1 (10.0)	3 (30.0)	2 (20.0)	1 (10.0)	0	0	7 (11.7)	3 (25.0)
Abnormal faeces	0	2 (20.0)	0	0	0	0	2 (3.3)	0
Diarrhoea	0	0	2 (20.0)	1 (10.0)	0	0	3 (5.0)	2 (16.7)
Dry mouth	0	0	0	0	0	0	0	1 (8.3)
Dyspepsia	0	1 (10.0)	0	0	0	0	1 (1.7)	0
Epigastric discomfort	0	0	0	0	0	0	0	1 (8.3)
Nausea	1 (10.0)	1 (10.0)	0	0	0	0	2 (3.3)	0
Vomiting	0	1 (10.0)	0	0	0	0	1 (1.7)	0
General disorders and administration site conditions								
-TOTAL	0	1 (10.0)	2 (20.0)	1 (10.0)	2 (20.0)	2 (20.0)	8 (13.3)	1 (8.3)
Chills	0	0	0	0	0	0	0	1 (8.3)
Feeling cold	0	0	1 (10.0)	0	0	0	1 (1.7)	0
Infusion site haematoma	0	0	0	0	1 (10.0)	0	1 (1.7)	0
Infusion site pain	0	0	0	0	1 (10.0)	2 (20.0)	3 (5.0)	0
Infusion site urticaria	0	0	0	0	0	1 (10.0)	1 (1.7)	0
Non-cardiac chest pain	0	1 (10.0)	0	0	0	0	1 (1.7)	0

Body system Preferred Term	SD-CHD APL180 1 mg (N=10)	SD-CHD APL180 3 mg (N=10)	SD-CHD APL180 10 mg (N=10)	SD-CHD APL180 30 mg (N=10)	SD-CHD APL180 60 mg (N=10)	SD-CHD APL180 100 mg (N=10)	SD-CHD All APL180 subjects (N=60)	SD-CHD Placebo (N=12)
Oedema peripheral	0	0	1 (10.0)	0	0	0	1 (1.7)	0
Pain	0	0	0	1 (10.0)	0	0	1 (1.7)	0
Swelling	0	0	0	1 (10.0)	0	0	1 (1.7)	0
Immune system disorders								
-TOTAL	0	1 (10.0)	0	0	0	0	1 (1.7)	0
Seasonal allergy	0	1 (10.0)	0	0	0	0	1 (1.7)	0
Infections and infestations								
-TOTAL	1 (10.0)	1 (10.0)	3 (30.0)	0	1 (10.0)	1 (10.0)	7 (11.7)	1 (8.3)
Anal abscess	0	0	0	0	0	1 (10.0)	1 (1.7)	0
Bronchitis	0	0	0	0	1 (10.0)	0	1 (1.7)	0
Escherichia urinary tract infection	1 (10.0)	0	0	0	0	0	1 (1.7)	0
Nasopharyngitis	0	1 (10.0)	0	0	0	0	1 (1.7)	0
Sinusitis	0	0	0	0	0	0	0	1 (8.3)
Skin candida	1 (10.0)	0	0	0	0	0	1 (1.7)	0
Upper respiratory tract infection	0	0	2 (20.0)	0	0	0	2 (3.3)	0
Urinary tract infection	0	0	1 (10.0)	0	0	0	1 (1.7)	0
Injury, poisoning and procedural complications								
-TOTAL	1 (10.0)	0	1 (10.0)	1 (10.0)	0	0	3 (5.0)	0
Contusion	1 (10.0)	0	0	1 (10.0)	0	0	2 (3.3)	0
Skin laceration	0	0	1 (10.0)	0	0	0	1 (1.7)	0
Investigations								
-TOTAL	0	1 (10.0)	1 (10.0)	0	3 (30.0)	1 (10.0)	6 (10.0)	1 (8.3)
Blood creatine phosphokinase increased	0	0	1 (10.0)	0	2 (20.0)	0	3 (5.0)	0

Body system Preferred Term	SD-CHD APL180 1 mg (N=10)	SD-CHD APL180 3 mg (N=10)	SD-CHD APL180 10 mg (N=10)	SD-CHD APL180 30 mg (N=10)	SD-CHD APL180 60 mg (N=10)	SD-CHD APL180 100 mg (N=10)	SD-CHD All APL180 subjects (N=60)	SD-CHD Placebo (N=12)
Blood glucose decreased	0	1 (10.0)	0	0	0	0	1 (1.7)	0
Blood pressure increased	0	0	0	0	0	1 (10.0)	1 (1.7)	0
Complement factor C3 decreased	0	0	0	0	0	0	0	1 (8.3)
Heart rate increased	0	0	0	0	0	1 (10.0)	1 (1.7)	0
Pancreatic enzymes increased	0	0	0	0	1 (10.0)	0	1 (1.7)	0
Metabolism and nutrition disorders								
-TOTAL	1 (10.0)	0	1 (10.0)	0	0	0	2 (3.3)	0
Gout	0	0	1 (10.0)	0	0	0	1 (1.7)	0
Hypoglycaemia	1 (10.0)	0	0	0	0	0	1 (1.7)	0
Musculoskeletal and connective tissue disorders								
-TOTAL	0	0	4 (40.0)	0	2 (20.0)	2 (20.0)	8 (13.3)	1 (8.3)
Arthralgia	0	0	0	0	1 (10.0)	0	1 (1.7)	0
Back pain	0	0	1 (10.0)	0	0	2 (20.0)	3 (5.0)	1 (8.3)
Muscle spasms	0	0	1 (10.0)	0	0	0	1 (1.7)	0
Musculoskeletal pain	0	0	1 (10.0)	0	0	0	1 (1.7)	0
Pain in extremity	0	0	1 (10.0)	0	0	0	1 (1.7)	0
Tendonitis	0	0	0	0	1 (10.0)	0	1 (1.7)	0
Nervous system disorders								
-TOTAL	1 (10.0)	2 (20.0)	2 (20.0)	1 (10.0)	1 (10.0)	1 (10.0)	8 (13.3)	2 (16.7)
Dizziness	0	0	2 (20.0)	0	0	0	2 (3.3)	0
Headache	1 (10.0)	2 (20.0)	0	1 (10.0)	0	1 (10.0)	5 (8.3)	2 (16.7)
Presyncope	0	0	0	0	1 (10.0)	0	1 (1.7)	0
Somnolence	0	0	2 (20.0)	0	0	0	2 (3.3)	0
Renal and urinary disorders								

Part III:

Body system Preferred Term	MD-CHD APL180 3 mg (N=6)	MD-CHD APL180 10 mg (N=6)	MD-CHD APL180 30 mg (N=26)	MD-CHD APL180 100 mg (N=6)	MD-CHD All APL180 subjects (N=44)	MD-CHD Placebo (N=28)
-Any Body System						
-TOTAL	3 (50.0)	2 (33.3)	13 (50.0)	5 (83.3)	23 (52.3)	17 (60.7)
Ear and labyrinth disorders						
-TOTAL	1 (16.7)	0	0	0	1 (2.3)	0
Ear discomfort	1 (16.7)	0	0	0	1 (2.3)	0
Eye disorders						
-TOTAL	0	0	1 (3.8)	0	1 (2.3)	0
Eye pruritus	0	0	1 (3.8)	0	1 (2.3)	0
Gastrointestinal disorders						
-TOTAL	0	0	4 (15.4)	2 (33.3)	6 (13.6)	3 (10.7)
Abdominal distension	0	0	0	0	0	1 (3.6)
Abdominal pain upper	0	0	0	0	0	1 (3.6)
Abdominal tenderness	0	0	0	0	0	1 (3.6)
Constipation	0	0	1 (3.8)	0	1 (2.3)	0
Diarrhoea	0	0	1 (3.8)	0	1 (2.3)	2 (7.1)
Dry mouth	0	0	0	1 (16.7)	1 (2.3)	0
Flatulence	0	0	0	1 (16.7)	1 (2.3)	1 (3.6)
Gingival pain	0	0	1 (3.8)	0	1 (2.3)	0
Nausea	0	0	1 (3.8)	0	1 (2.3)	0
Vomiting	0	0	0	0	0	1 (3.6)
General disorders and administration site conditions						
-TOTAL	2 (33.3)	0	4 (15.4)	4 (66.7)	10 (22.7)	4 (14.3)
Application site erythema	0	0	0	1 (16.7)	1 (2.3)	1 (3.6)

Body system Preferred Term	MD-CHD APL180 3 mg (N=6)	MD-CHD APL180 10 mg (N=6)	MD-CHD APL180 30 mg (N=26)	MD-CHD APL180 100 mg (N=6)	MD-CHD All APL180 subjects (N=44)	MD-CHD Placebo (N=28)
Catheter site pain	0	0	1 (3.8)	0	1 (2.3)	0
Feeling cold	1 (16.7)	0	0	0	1 (2.3)	0
Infusion related reaction	1 (16.7)	0	0	0	1 (2.3)	0
Infusion site erythema	1 (16.7)	0	0	1 (16.7)	2 (4.5)	2 (7.1)
Infusion site haematoma	1 (16.7)	0	0	1 (16.7)	2 (4.5)	1 (3.6)
Infusion site pain	0	0	2 (7.7)	2 (33.3)	4 (9.1)	2 (7.1)
Infusion site swelling	0	0	0	1 (16.7)	1 (2.3)	0
Injection site discomfort	0	0	1 (3.8)	0	1 (2.3)	0
Injection site pruritus	0	0	0	0	0	1 (3.6)
Oedema peripheral	1 (16.7)	0	2 (7.7)	0	3 (6.8)	1 (3.6)
Infections and infestations						
-TOTAL	1 (16.7)	0	2 (7.7)	0	3 (6.8)	0
Cellulitis	0	0	1 (3.8)	0	1 (2.3)	0
Nasopharyngitis	0	0	1 (3.8)	0	1 (2.3)	0
Upper respiratory tract infection	1 (16.7)	0	0	0	1 (2.3)	0
Injury, poisoning and procedural complications						
-TOTAL	0	0	1 (3.8)	2 (33.3)	3 (6.8)	4 (14.3)
Animal bite	0	0	0	0	0	1 (3.6)
Contusion	0	0	1 (3.8)	2 (33.3)	3 (6.8)	2 (7.1)
Muscle strain	0	0	0	0	0	1 (3.6)
Investigations						
-TOTAL	1 (16.7)	0	0	0	1 (2.3)	0
Haemoglobin decreased	1 (16.7)	0	0	0	1 (2.3)	0

Body system Preferred Term	MD-CHD APL180 3 mg (N=6)	MD-CHD APL180 10 mg (N=6)	MD-CHD APL180 30 mg (N=26)	MD-CHD APL180 100 mg (N=6)	MD-CHD All APL180 subjects (N=44)	MD-CHD Placebo (N=28)
Musculoskeletal and connective tissue disorders						
-TOTAL	1 (16.7)	2 (33.3)	3 (11.5)	2 (33.3)	8 (18.2)	8 (28.6)
Arthralgia	0	0	1 (3.8)	0	1 (2.3)	0
Back pain	0	0	0	0	0	3 (10.7)
Bursitis	0	1 (16.7)	0	0	1 (2.3)	0
Flank pain	0	0	0	0	0	1 (3.6)
Muscle spasms	0	0	1 (3.8)	0	1 (2.3)	1 (3.6)
Musculoskeletal pain	0	1 (16.7)	0	1 (16.7)	2 (4.5)	0
Pain in extremity	1 (16.7)	0	2 (7.7)	2 (33.3)	5 (11.4)	3 (10.7)
Nervous system disorders						
-TOTAL	2 (33.3)	1 (16.7)	5 (19.2)	1 (16.7)	9 (20.5)	7 (25.0)
Cerebrovascular accident	0	0	0	1 (16.7)	1 (2.3)	0
Dizziness	0	0	1 (3.8)	0	1 (2.3)	3 (10.7)
Dysgeusia	1 (16.7)	0	0	0	1 (2.3)	0
Headache	1 (16.7)	1 (16.7)	3 (11.5)	0	5 (11.4)	4 (14.3)
Paraesthesia	0	0	2 (7.7)	0	2 (4.5)	0
Presyncope	1 (16.7)	0	0	0	1 (2.3)	0
Restless legs syndrome	0	0	0	0	0	1 (3.6)
Skin and subcutaneous tissue disorders						
-TOTAL	0	1 (16.7)	1 (3.8)	2 (33.3)	4 (9.1)	3 (10.7)
Erythema	0	0	1 (3.8)	0	1 (2.3)	1 (3.6)
Pruritus	0	1 (16.7)	0	0	1 (2.3)	0
Rash pruritic	0	0	0	0	0	1 (3.6)
Skin depigmentation	0	0	0	1 (16.7)	1 (2.3)	0
Skin discoloration	0	0	0	1 (16.7)	1 (2.3)	1 (3.6)
Vascular disorders						
-TOTAL	1 (16.7)	1 (16.7)	2 (7.7)	0	4 (9.1)	0
Hematoma	0	0	2 (7.7)	0	2 (4.5)	0
Hypertension	1 (16.7)	0	0	0	1 (2.3)	0
Phlebitis	0	1 (16.7)	0	0	1 (2.3)	0

	Novartis product	***Comparator***
No. (%) of subjects studied	*128*	*44*
Number (%) of subjects with serious or other significant events	*n (%)*	*n (%)*
Death	*0 (0.0)*	*0 (0.0)*
SAE(s)	*2 (0.01%)*	*0 (0.0)*
Discontinued due to SAE(s)	*0 (0.0)*	*0 (0.0)*

SAEs: one perianal abscess, one vertebro-basilar cerebrovascular accident

Other Relevant Findings

APL180 did not produce an immunogenic response after single or multiple dosing.

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