**Appendix 1. Study centers and investigators.**

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| **Site** | **Investigator** | **Clinic/Hospital** |
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| 1002 | Yanli Yang 杨燕丽 |
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|  |  |  |
| --- | --- | --- |
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|  | Hao Fu 符 浩 |
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| 1003 | Wenli Chen 陈文利  Lan Lin 林 岚 |
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| 1008 | Hong Mao (Principal Investigator)  毛红 (PI)  Chen Cheng 程 晨Zhongjin Wang 王中京Shi Zhao 赵 湜  Ling Zhou 周 玲 | The Central Hospital of Wuhan  No. 26 Shengli Street, Jiangan District  Wuhan City  Hubei 430014 China  武汉市中心医院  江岸区胜利街 26 号武汉市  湖北省 430014  中国 |
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| 1021 | Fangping Li (Principal Investigator before 18Dec2018)  李芳萍（2018 年 12 月 18 日之前的  PI）  Muchao Wu (Principal Investigator after 18Dec2018)  吴木潮（2018 年 12 月 18 日之后的  PI） | Sun Yat-sen Memorial Hospital  Sun Yat-sen University  No. 107 Yanjiang West Road  Guangzhou City  Guangdong 510120 China  中山大学孙逸仙纪念医院沿江西路 107 号  广州市  广东省 510120 |
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**Supplementary Table 1.**

**Baseline lipid and lipoprotein parameters in the mHTG and combined treatment cohorts. Data are expressed as mean (SD) for full subject sample. Baseline = last available observation prior to first administration of study drug.**

|  |  |  |  |
| --- | --- | --- | --- |
| **MODERATE TRIGLYCERIDE MONOTHERAPY COHORT** | | | |
|  | OMACOR (N=47) | PLACEBO (N=48) | All subjects (N=95) |
| Triglycerides (mg/dL) | 354.5 (85.6) | 330.1 (71.2) | 342.2 (79.2) |
| Total cholesterol (mg/dL) | 199.5 (35.9) | 188.8 (32.7) | 194.1 (34.6) |
| HDL-C (mg/dL) | 38.3 (7.8) | 36.4 (8.1) | 37.3 (7.9) |
| LDL-C (mg/dL) | 125.8 (37.4) | 121.6 (31.7) | 123.7 (34.5) |
| Non-HDL cholesterol (mg/dL) | 161.2 (34.3) | 152.4 (28.9) | 156.8 (31.8) |
| LDL-C/HDL-C ratio | 3.419 (1.404) | 3.409 (0.818) | 3.414 (1.140) |
| **CO-ADMINISTRATION OF STATIN COHORT** | | | |
|  | OMACOR (N=40) | PLACEBO (N=35) | All subjects (N=75) |
| Triglycerides (mg/dL) | 395.8 (146.0) | 406.5 (135.1) | 400.8 (140.2) |
| Total cholesterol (mg/dL) | 170.7 (44.3) | 178.0 (56.8) | 174.1 (50.3) |
| HDL-C (mg/dL) | 38.8 (7.2) | 36.9 (6.4) | 37.9 (6.9) |
| LDL-C (mg/dL) | 88.9 (35.8) | 93.8 (51.4) | 91.1 (43.5) |
| Non-HDL cholesterol (mg/dL) | 131.9 (41.4) | 141.1 (57.5) | 136.2 (49.4) |
| LDL-C/HDL-C ratio | 2.267 (0.750) | 2.622 (1.562) | 2.433 (1.204) |

**Supplementary Table 2.**

**Concomitant medication ≥12% in at least one treatment assignment at baseline in the OM3EE/statin cohort. Data are expressed as number of patients (%). Percentages are based on the number of subjects in the full analysis subject sample.**

|  |  |  |  |
| --- | --- | --- | --- |
| **ATC third-level subgroup code (ATC code)**  **Preferred name WHO DD** | **OMACOR (n=40)** | **PLACEBO (n=35)** | **All SUBJECTS (n=75)** |
| LIPID-MODIFYING AGENTS, PLAIN (C1OA) | 40 (100.0) | 35 (100.0) | 75 (100.0) |
| *ATORVASTATIN CALCIUM* | 11 (27.5) | 14 (40.0) | 25 (33.3) |
| *ATORVASTATIN* | 9 (22.5) | 4 (11.4) | 13 (17.3) |
| *ROSUVASTATIN CALCIUM* | 8 (20.0) | 5 (14.3) | 13 (17.3) |
| *ROSUVASTATIN* | 5 (12.5) | 5 (14.3) | 10 (13.3) |
| ANTITHROMBOTIC AGENTS (B01A) | 23 (57.5) | 26 (74.3) | 49 (65.3) |
| *ACETYLSALICYLIC ACID* | 17 (42.5) | 20 (57.1) | 37 (49.3) |
| *CLOPIDOGREL BISULFATE* | 8 (20.0) | 8 (22.9) | 16 (21.3) |
| UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE (V90) | 21 (52.5) | 12 (34.3) | 33 (44.0) |
| *TRADITIONAL MEDICINE* | 20 (50.0) | 11 (31.4) | 31 (41.3) |
| BETA-BLOCKING AGENTS (C07A) | 13 (32.5) | 18 (51.4) | 31 (41.3) |
| *METOPROLOL SUCCINATE* | 3 (7.5) | 11 (31.4) | 14 (18.7) |
| SELECTIVE CALCIUM-CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS (C08C) | 15 (37.5) | 15 (42.9) | 30 (40.0) |
| *AMLODIPINE BESILATE* | 5 (12.5) | 8 (22.9) | 13 (17.3) |
| *NIFEDIPINE* | 6 (15.0) | 6 (17.1) | 12 (16.0) |
| BLOOD GLUCOSE-LOWERING DRUGS, EXCL. INSULINS (A10B) | 13 (32.5) | 14 (40.0) | 27 (36.0) |
| *METFORMIN HYDROCHLORIDE* | 7 (17.5) | 8 (22.9) | 15 (20.0) |
| *ACARBOSE* | 7 (17.5) | 4 (11.4) | 11 (14.7) |
| ANGIOTENSIN II ANTAGONISTS, COMBINATIONS PLAIN (C09C) | 13 (32.5) | 10 (28.6) | 23 (30.7) |
| *IRBESARTAN* | 7 (17.5) | 4 (11.4) | 11 (14.7) |
| OTHER CARDIAC PREPARATIONS (C01E) | 6 (15.0) | 3 (8.6) | 9 (12.0) |
| VITAMIN B12 AND FOLIC ACID (B03B) | 4 (10.0) | 5 (14.3) | 9 (12.0) |
| ACE INHIBITORS, PLAIN (C09A) | 2 (5.0) | 6 (17.1) | 8 (10.7) |
| ANGIOTENSIN II ANTAGONISTS (C09D) | 5 (12.5) | 3 (8.6) | 8 (10.7) |

**Supplementary Table 3.**

**Mean percentage triglyceride effect of OM3EE in the mHTG and combined treatment cohorts. Full analysis subject sample.**

|  |  |  |  |
| --- | --- | --- | --- |
| **MODERATE TRIGLYCERIDE MONOTHERAPY COHORT** | | | |
| Visit | Statistic | OMACOR (n=47) | PLACEBO (N=48) |
| Baseline | Mean (SD)  Median  Min/Max | 354.5 (85.6)  372.0  204/492 | 330.1 (71.2)  317.0  222/498 |
| End of treatment | Mean (SD)  Median  Min/Max | 308.0 (175.9) 262.0  85/1030 | 506.4 (431.5)  324.5  168/2288 |
| Change from baseline | Mean (SD)  Median  Min/Max | –46.5 (165.7)  –49.0  –291/576 | 176.3 (426.3)  52.5  –290/1914 |
| Percent change from baseline | Mean (SD)  Median  Min/Max | –12.12 (47.22)  –19.51  –72.1/151.8 | 55.46 (130.94)  17.61  –63.3/549.6 |
| **CO-ADMINISTRATION OF STATIN COHORT** | | | |
| Visit | Statistic | OMACOR (n=40) | PLACEBO (n=35) |
| Baseline | Mean (SD)  Median  Min/Max | 395.8 (146.0) 360.5  210/708 | 406.5 (135.1)  392.0  218/814 |
| End of treatment | Mean (SD)  Median  Min/Max | 282.0 (140.9) 254.5  96/708 | 403.8 (216.3)  381.0  110/989 |
| Change from baseline | Mean (SD)  Median  Min/Max | –113.8 (174.0)  –96.5  –563/235 | –2.8 (234.7)  –36.0  –437/592 |
| Percent change from baseline | Mean (SD)  Median  Min/Max | –23.25 (40.00)  –31.80  –79.5/100.4 | 6.24 (63.17)  –11.92  –66.8/198.2 |

**Supplementary Table 4.**

**Effects of OM3EE therapy on non-TG lipid and lipoprotein indices in the mHTG and combined treatment cohorts.** **ANCOVA results for percent changes in total cholesterol, LDL-C, HDL-C, non-HDL-C and LDL-C/HDL-C ratio.**

1. **Moderate triglyceride monotherapy cohort**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | No. of patients | LS means | Standard error | 95% CI | P-value |
| **Total cholesterol** |  |  |  |  |  |
| *Placebo* | 48 | 9.09 | 2.75 | 3.61/14.57 |  |
| *Omacor* | 47 | 2.57 | 2.78 | –2.97/8.11 |  |
| *Omacor–placebo* | 95 | –6.52 | 3.96 | –14.40/1.35 | 0.1031 |
| **LDL-cholesterol** |  |  |  |  |  |
| *Placebo* | 48 | –3.67 | 3.28 | –10.20/2.86 |  |
| *Omacor* | 47 | 4.96 | 3.32 | –1.65/11.56 |  |
| *Omacor–placebo* | 95 | 8.63 | 4.69 | –0.71/17.96 | 0.0697 |
| **HDL-cholesterol** |  |  |  |  |  |
| *Placebo* | 48 | –0.04 | 2.72 | –5.46/5.38 |  |
| *Omacor* | 47 | 2.86 | 2.75 | –2.62/8.34 |  |
| *Omacor–placebo* | 95 | 2.90 | 3.90 | –4.87/10.67 | 0.4603 |
| **Non-HDL cholesterol** |  |  |  |  |  |
| *Placebo* | 48 | 11.58 | 3.51 | 4.58/18.57 |  |
| *Omacor* | 47 | 2.81 | 3.55 | –4.26/9.88 |  |
| *Omacor–placebo* | 95 | -8.77 | 5.04 | –18.80/1.27 | 0.0859 |
| **LDL-C/HDL-C ratio** |  |  |  |  |  |
| *Placebo* | 48 | –3.98 | 3.16 | –10.27/2.30 |  |
| *Omacor* | 47 | 4.00 | 3.19 | –2.35*I*10.35 |  |
| *Omacor–placebo* | 95 | 7.98 | 4.51 | –0.99/16.96 | 0.0806 |

1. **Co-administration of statin cohort**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Patients (No.) | LS Means | Standard Error | 95% CI | P-value |
| **Total cholesterol** |  |  |  |  |  |
| *Placebo* | 35 | 3.01 | 3.36 | –3.71/9.73 |  |
| *Omacor* | 40 | –4.60 | 3.14 | –10.88/1.67 |  |
| *Omacor–placebo* | 75 | –7.61 | 4.66 | –16.94/1.72 | 0.1081 |
| **LDL-cholesterol** |  |  |  |  |  |
| *Placebo* | 35 | 7.20 | 4.31 | –1.43/15.83 |  |
| *Omacor* | 40 | 5.58 | 4.03 | –2.48/13.64 |  |
| *Omacor–placebo* | 75 | –1.62 | 5.98 | –13.59/10.35 | 0.7876 |
| **HDL-cholesterol** |  |  |  |  |  |
| *Placebo* | 35 | 4.61 | 2.77 | –0.93/10.15 |  |
| *Omacor* | 40 | 4.75 | 2.58 | –0.42/9.91 |  |
| *Omacor–placebo* | 75 | 0.14 | 3.87 | –7.60/7.88 | 0.9712 |
| **Non-HDL cholesterol** |  |  |  |  |  |
| *Placebo* | 35 | 3.81 | 4.76 | –5.71/13.33 |  |
| *Omacor* | 40 | –6.96 | 4.44 | –15.84/1.93 |  |
| *Omacor–placebo* | 75 | –10.77 | 6.62 | –24.01/2.47 | 0.1090 |
|  |  |  |  |  |  |
| **LDL-C/HDL-C ratio** |  |  |  |  |  |
| *Placebo* | 35 | 4.04 | 4.64 | –5.25/13.32 |  |
| *Omacor* | 40 | 2.32 | 4.33 | –6.34/10.98 |  |
| *Omacor–placebo* | 75 | –1.72 | 6.46 | –14.65/11.22 | 0.7915 |

**Supplementary Table 5.**

**Summary of adverse events stratified by treatment assignment. Percentages are based on the number of patients in the safety sample or in the respective cohorts.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **OMACOR** | | | **PLACEBO** | | |
| N | % | E | N | % | E |
| **Number of patients in safety sample** | 126 |  |  | 122 |  |  |
| *High TG monotherapy cohort* | 39 |  |  | 37 |  |  |
| *Moderate TG monotherapy cohort* | 47 |  |  | 49 |  |  |
| *Co-administration cohort* | 40 |  |  | 36 |  |  |
|  |  |  |  |  |  |  |
| **Deaths** | 0 | 0 | 0 | 0 | 0 | 0 |
|  |  |  |  |  |  |  |
| **At least one SAE** | 12 | 9.5 | 18 | 6 | 4.9 | 7 |
| *High TG monotherapy cohort* | 5 | 12.8 | 7 | 1 | 2.7 | 1 |
| *Moderate TG monotherapy cohort* | 4 | 8.5 | 7 | 3 | 6.1 | 4 |
| *Co-administration cohort* | 3 | 7.5 | 4 | 2 | 5.6 | 2 |
| **At least one TESAE** | 9 | 7.1 | 14 | 4 | 3.3 | 5 |
| *High TG monotherapy cohort* | 3 | 7.7 | 5 | 0 | 0 | 0 |
| *Moderate TG monotherapy cohort* | 3 | 6.4 | 5 | 2 | 4.1 | 3 |
| *Co-administration cohort* | 3 | 7.5 | 4 | 2 | 5.6 | 2 |
| **At least one TEAE leading to study termination\*** | 2 | 1.6 | 2 | 4 | 3.3 | 4 |
| *High TG monotherapy cohort* | 2 | 5.1 | 2 | 1 | 2.7 | 1 |
| *Moderate TG monotherapy cohort* | 0 | 0 | 0 | 2 | 4.1 | 2 |
| *Co-administration cohort* | 0 | 0 | 0 | 1 | 2.8 | 1 |
| **At least one TEAE** | 59 | 46.8 | 113 | 69 | 56.6 | 122 |
| *High TG monotherapy cohort* | 21 | 53.8 | 40 | 24 | 64.9 | 41 |
| *Moderate TG monotherapy cohort* | 19 | 40.4 | 43 | 24 | 49.0 | 44 |
| *Co-administration cohort* | 19 | 47.5 | 30 | 21 | 58.3 | 37 |
| **At least one severe TEAE\*\*** | 10 | 7.9 | 14 | 7 | 5.7 | 8 |
| *High TG monotherapy cohort* | 2 | 5.1 | 3 | 3 | 8.1 | 3 |
| *Moderate TG monotherapy cohort* | 5 | 10.6 | 7 | 3 | 6.1 | 4 |
| *Co-administration cohort* | 3 | 7.5 | 4 | 1 | 2.8 | 1 |
| **At least one TEAE with a reasonable possibility of causal relationship\*\*\*** | 8 | 6.3 | 9 | 15 | 12.3 | 17 |
| *High TG monotherapy cohort* | 3 | 7.7 | 3 | 5 | 13.5 | 6 |
| *Moderate TG monotherapy cohort* | 3 | 6.4 | 3 | 3 | 6.1 | 3 |
| *Co-administration cohort* | 2 | 5.0 | 3 | 7 | 19.4 | 8 |
| **Number of patients without any TEAEs** | 67 | 53.2 |  | 53 | 43.4 |  |
| *High TG monotherapy cohort* | 18 | 46.2 |  | 13 | 35.1 |  |
| *Moderate TG monotherapy cohort* | 28 | 59.6 |  | 25 | 51.0 |  |
| *Co-administration cohort* | 21 | 52.5 |  | 15 | 41.7 |  |

**N = number of patients; E = number of events.**

**\*TEAEs leading to study termination = TEAEs reported on the adverse events CRF as “Led to study termination” = “yes”.**

**\*\*Severe = severity reported as “severe” or missing.**

**\*\*\*“Reasonable possibility of causal relationship” = drug-event relationship recorded as “possible”, “probable” or missing.**