SUPPLEMENTARY MATERIAL

Efficacy and safety of evolocumab in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia: 12-week primary results of the HUA TUO 华佗 randomized clinical trial

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Appendix A – Committees, Leadership, and Investigators

List of investigators and institutional review boards/independent ethics committees

This study was conducted at 31 study centers in China. Principal investigators are listed below by the number of patients enrolled.

Principal investigator	Site name (site number)	Reference Number	Site address
Jiyan Chen	Guangdong Provincial People's Hospital (18005)	粤医伦理【2018】11号	No. 106 Zhongshan Er Road, Yuexiu District, Guangdong General Hospital, Guangzhou, Guangdong, 510080, China
Weimin Li	The First Affiliated Hospital of Harbin Medical University (18010)	哈医一伦审201801	23 Youzheng Street, Nangang District, Harbin, Heilongjiang, 150001, China

Zhouqing Huang	The First Affiliated Hospital of Wenzhou Medical University (18044)	临床研究（药/械）伦审（2018）第（107）号	South Nanbaixiang Shangcai Village, Ouhai District, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325000, China
Yajun Han	Inner Mongolia People's Hospital (18013)	YWLCSYLL2018-004-01	20 Zhaowuda Road, Huhehaote, Nei Mongolia, 010017, China
Xuecheng Huang	The Second Nanning People's Hospital (18054)	2018008	No. 13 Dancun Road, Jiangnan District, Nanning, Guangxi, 530031, China
Dongye Li	The Affiliated Hospital of Xuzhou Medical University (18024)	XYFY2018-YL062-01	No. 99 West Huaihai Road, The Affiliated Hospital of Xuzhou Medical College, Xuzhou, Jiangsu, 221006, China
Xiaochun Xing	Tianjin Fourth Centre Hospital (18061)	SZXLL-2018-016	No. 1 Zhongshan Road, Hebei District, Tianjin, 300140, China

Luping Jiang	Changsha Central Hospital (18026)	长沙市中心医院伦理药械审[2018]006号	No. 161 South Shaoshan Road, Yuhua District, Changsha Central Hospital, Changsha, Hunan, 410004, China
Zhen Wang	Changsha Central Hospital (18027)	长沙市中心医院伦理药械审[2018]007号	No. 161 South Shaoshan Road, Yuhua District, Changsha Central Hospital, Changsha, Hunan, 410004, China
Zhanquan Li	The People's Hospital of Liaoning Province (18011)	(2018)伦审药第(HS010)号	No. 33 Wenyi Road, Shenhe District, The People's Hospital of Liaoning Province, Shenyang, Liaoning, 110016, China
Peijing Liu	Affiliated Hospital of Jiangsu University (18064)	(2019)伦审第（31）号	No. 438 Jiefang Road, Jingkou District, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, 212001, China

Shuguang Pang	Jinan Central Hospital (18038)	济中心伦理临审2018-051-01号	No. 105 Jiefang Road, Lixia District, Jinan Central Hospital, Jinan, Shandong, 250013, China
Guohai Su	Jinan Central Hospital (18039)	济中心伦理临审2018-038-01号	No. 105 Jiefang Road, Lixia District, Jinan Central Hospital, Jinan, Shandong, 250013, China
Jingfeng Wang	Sun Yat-sen Memorial Hospital Sun Yatsen University (18040)	2018快审第（160）号	No. 107 West Yan Jiang Road, Yuexiu District, Guangzhou, Guangdong, 510120, China
Qinghua Wu	The Second Affiliated Hospital to Nanchang University (18041)	药临审【2018】第（12）号	No. 1 Minde Road, Donghu District, The Second Affiliated Hospital To Nanchang University, Nanchang, Jiangxi, 330006, China

Weihong Jiang	The Third Xiangya Hospital of Central South University (18021)	快18207	No. 138 Tongzipo Road, Yuelu District, The Third Xiangya Hospital of Central South University, Changsha, Hunan, 410013, China
Zhaoping Li	Peking University Third Hospital (18046)	（2018）药伦审第（066-02）号	No. 49 North Garden Road, Haidian District, Peking University Third Hospital, Beijing, Beijing, 100191, China
Feng Liu	Suzhou Kowloon Hospital (18043)	九龙伦审 YC-2018-002	No. 118 Wansheng Street, Suzhou Kowloon Hospital, Suzhou, Jiangsu, 215000, China
Lijuan Wang	Guangdong Provincial People's Hospital (18047)	粤医伦理【2018】12-1号	No. 106 Zhongshan Er Road, Yuexiu District, Guangdong General Hospital, Guangzhou, Guangdong, 510080, China

Daoquan Peng	The Second Xiangya Hospital of Central South University (18020)	（2018）伦审【药】第(087)号	No. 139 Middle Renmin Road, Furong District, Changsha, Hunan, 410011, China
Jing Yan	Zhejiang Hospital (18055)	2018临审第（13G）	No. 12 Lingyin Road, Xihu District, Hangzhou, Zhejiang, 310013, China
Hanbin Cui	Ningbo First Hospital (18063)	2018-D002	No. 59 Liuting Street, Haishu District, Ningbo First Hospital, Ningbo, Zhejiang, 315010, China
Li Li	Guangzhou Red Cross Hospital (18048)	穗红院医伦审2018-074-01	No. 396 Tongfu Road, Haizhu District, Guangzhou, Guangdong, 510220, China
Yafei Mi	Taizhou Hospital of Zhejiang Province (18058)	201812-01	No. 150 Ximen Road, 9F, Inpatient Building, Linhai, Zhejiang, 317000, China

Fang Wang	Beijing Hospital (18050)	2018BJYYEC-095-01	No. 1 Dongdan Dahua Road, Dongcheng District, Beijing, Beijing, 100730, China
Yuanming Wang	Shanghai Yangpu District Central Hospital (18062)	LL-2018-DZX-015	No. 450 Tengyue Street, Yangpu District, Shanghai, Shanghai, 200090, China
Chun Wu	Peking University Shenzhen Hospital (18015)	北大深医伦审[2018]第（005）号	No. 1120 Lianhua Road, Futian District, Shenzhen, Guangdong, 518036, China
Liming Zhang	The First Affiliated Hospital of Harbin Medical University (18019)	哈医一伦审201802	23 Youzheng Street, Nangang District, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, 150001, China
Yuemin Sun	Tianjin Medical University	IRB2018-054-01	No. 154 Anshan Road, Heping District, Tianjin Medical University

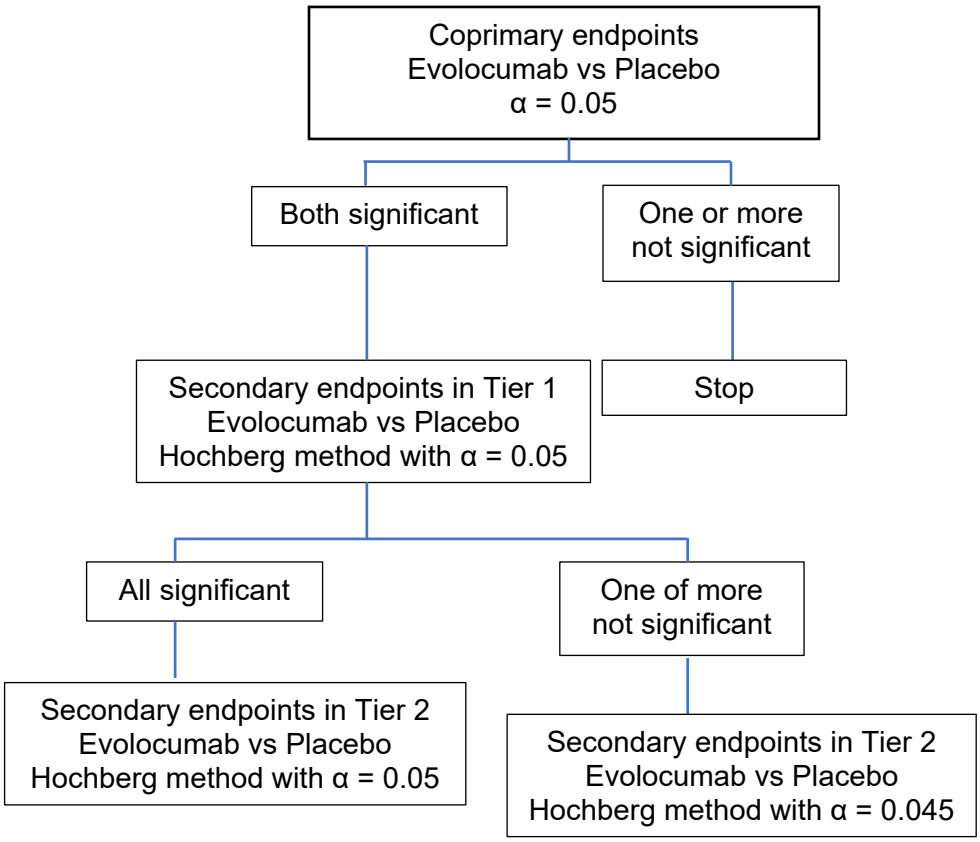
	General Hospital (18022)		General Hospital, Tianjin, 300052, China
Ping Yang	China-Japan Union Hospital of Jilin University (18025)	(2018年)临审第（2018062802）号	126 Xiantai Street, Economic-Technological Development District, China-Japan Union Hospital of Jilin University, Changchun, Jilin, 130033, China
Zuyi Yuan	The First Affiliated Hospital of Xi An Jiao Tong University (18023)	2019伦审药临字第（7）号	No. 277 West Yanta Road, Yanta District, Xi An, Shanxi, 710061, China

Xiaoyun Zeng	Wuhan Puai Hospital (18004)	伦审字（YW2018-008-01）号	473 Hanzheng Street, Qiaokou District, Wuhan Puai Hospital, Wuhan, Hubei, 430030, China
Qiang Dong	Huashan Hospital Affiliated to Fudan University (18036)	（2018）临审第（383）号	No. 12 Middle Urumqi Road, Jingan District, Shanghai, 200040, China
Xiaoping Pan	Guangzhou First Peoples Hospital (18006)	A-2018-007-02	No. 1 Panfu Road, Yuexiu District, Guangzhou, Guangdong, 510180, China
Guogang Zhang	Xiangya Hospital Central South University (18034)	伦审快第（201809131）号	No. 87 Xiangya Road, Kaifu District, Changsha, Hunan, 410008, China

Appendix B – Supplemental Methods

Exploratory endpoints

Exploratory endpoints included the mean percent change from baseline in apolipoprotein A1 (ApoA1) at weeks 10 and 12; percent change from baseline in ApoA1 at week 12; change from baseline in high-sensitivity C-reactive protein; change from baseline in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels at each scheduled assessment; and change and percent change from baseline at each scheduled visit for each of the following lipid parameters: LDL-C, total cholesterol, non-HDL-C, ApoB, VLDL-C, HDL-C, ApoA1, triglycerides, and lipoprotein a [Lp(a)].



Online Figure 1. Multiplicity adjustment method. Shown here is the multiplicity adjustment method for the primary and secondary endpoints to preserve the family-wise error rate of 0.05 using sequential gatekeeping and Hochberg procedures.[1] Tier 1 includes the mean change from baseline at weeks 10 and 12 and the change from baseline at week 12 for LDL-C, non-HDL-C (percent change), ApoB (percent change), total cholesterol (percent change), achievement of target LDL-C (<70 mg/dL [1.8 mmol/L]), LDL-C response (≥50% reduction from baseline in LDL-C). Tier 2 includes the mean change from baseline at weeks 10 and 12 and the change from baseline at week 12 for Lp(a) (percent change), triglycerides (percent change), HDL-C (percent change), and VLDL-C (percent change). ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); VLDL-C, very low-density lipoprotein.

Appendix C – Supplemental Results

Table S1. Eligibility criteria

Inclusion criteria

- ≥18 years of age at signing of informed consent form
- Approved statin (with or without ezetimibe) at optimal and stable daily dose(s) (not requiring uptitration according to investigator) for ≥4 weeks before LDL-C screening
- Fasting LDL-C at screening ≥80 mg/dL (2.1 mmol/L) as determined by central laboratory
- Patient meets ≥1 of the following for high/very high cardiovascular risk:
    - history of CAD or ischemic stroke
    - diagnosis of PAD
    - eGFR at screening of ≥ 30 to < 60 mL/min/1.73 m^2
    - diagnosis of diabetes mellitus type 2
    - presence of ≥ 3 of the following risk factors:
        - ≥ 45 years of age for males; ≥ 55 years of age for females
        - hypertension
        - smoking
        - family history of premature CVD (first degree of relative; male < 55 years, females < 65 years)

- HDL-C < 40 mg/dL (1.0 mmol/L)
- BMI ≥ 28 kg/m^2

OR

- Patient does not meet high/very high CV risk criteria but has a fasting LDL-C at screening of ≥ 130 mg/dL (3.4 mmol/L)
- Fasting triglycerides at screening ≤ 400 mg/dL (4.5 mmol/L) as determined by the central laboratory
- Patient tolerates placebo injection at screening

Exclusion criteria

- Myocardial infarction, unstable angina, PCI, CABG, or stroke within 3 months before randomization
- Planned coronary or other revascularization within 20 weeks of screening
- NYHA III or IV heart failure, or last known left ventricular ejection fraction <30
- Uncontrolled serious cardiac arrhythmia defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia that are not controlled by medications, in the past 3 months before randomization
- Type 1 diabetes, new-onset (hemoglobin [Hb]A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL at screening without known diagnosis) or poorly controlled (HbA1c ≥8.5%) type 2 diabetes, as determined by central laboratory at screening
- Uncontrolled hypertension defined as sitting SBP >180 mmHg or DBP >110 mmHg
- Use of a CETP inhibitor in the 12 months before randomization

- Patient has taken one of the following in the 6 weeks before LDL-C screening: red yeast rice, >200 mg/day niacin, >1000 mg/day omega-3 fatty acids (eg, dihydroxyacetone docosahexaenoic acid and eicosapentaenoic acid), stanols or prescription lipid-regulating drugs (eg, bile-acid sequestering resins, fibrates and derivatives), or other cholesterol-lowering drugs, or lipid-lowering dietary supplements, or food additives other than statins and ezetimibe
- Treatment 3 months before LDL-C screening with any of the following drugs: systemic cyclosporine, systemic steroids (IV, IM, or PO; hormone replacement therapy was permitted), vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane; vitamin A in a multivitamin preparation was permitted)
- Uncontrolled hypothyroidism or hyperthyroidism as defined by TSH <1 x LLN or >1.5 x ULN, respectively, at screening
- Severe renal dysfunction, defined as an eGFR < 30 mL/min/1.73 m^2 at screening as estimated by the Cockcroft-Gault method
- Active liver disease or hepatic dysfunction, defined as AST or ALT >3 x ULN as determined by central laboratory analysis at screening
- CK >5 x ULN at screening
- Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the past 5 years before randomization
- Prior treatment with evolocumab or any other PCSK9 inhibitor
- Known sensitivity to any of the active substances or their excipients to be administered during dosing (eg, carboxymethylcellulose)

- Inability of the patient to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the patient and investigator's knowledge
- History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion
- Current treatment with another investigational device or drug study, or <30 days before randomization since ending treatment on another investigational device or drug study(s) or planning to receive other investigational procedures while participating in this study
- Female patients of childbearing potential not willing to use an acceptable method(s) of effective birth control during treatment with IP and for an additional 15 weeks after the end of treatment with the IP
- Female patients of non-childbearing potential who are not required to use contraception during the study and include those who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or who are postmenopausal
- Female patient who is pregnant or nursing, planning to become pregnant or planning to nurse during treatment with IP and/or within 15 weeks after the end of treatment with IP

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CETP, cholesterylester transfer protein; CK, creatinine kinase; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IM, intramuscular; IP, investigational product; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLN, lower limit of normal; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; PO, oral; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Table S2. Results of other efficacy endpoints

Endpoint	Evolocumab 140 mg SC Q2W (N = 79)	Placebo SC Q2W (N = 41)	Evolocumab 420 mg SC QM (N = 80)	Placebo SC QM (N = 41)
Mean percent change from baseline in triglycerides at weeks 10 and 12, 95% CI*, %	–9.9 (–18.2, –1.6)	5.2 (–4.2, 14.7)	–16.6 (–24.7, –8.6)	3.0 (–6.6, 12.6)
Difference*,**	**–15.1 (–24.4 to –5.8)** *P* = 0.002		**–19.7 (–28.3 to –11.1)** *P* < 0.0001	
Percent change from baseline in triglycerides at week 12, 95% CI*, %	–7.6 (–16.9, 1.8)	10.0 (–1.1, 21.2)	–11.7 (–20.3, –3.0)	0.7 (–10.3, 11.7)
Difference*,**	**–17.6 (–29.4 to –5.7)** *P* = 0.004		**–12.4 (–23.0 to –1.7)** *P* =0.02	
Mean change from baseline in HDL-C at weeks 10 and 12, 95% CI*, mg/dL	9.5 (4.8, 14.1)	1.0 (–4.2, 6.3)	8.7 (4.3, 13.0)	1.9 (–3.3, 7.0)
Difference*,**	**8.4 (3.4 to 13.5)** *P* = 0.001		**6.8 (2.1 to 11.5)** *P* =0.005	

Change from baseline in HDL-C at week 12,				
95% CI*, mg/dL	9.9	2.0	7.1	1.0
	(5.0, 14.8)	(–3.8, 7.7)	(2.5, 11.7)	(–4.9, 6.8)
Difference*,**	**7.9 (2.2 to 13.7)**		**6.2 (0.4 to 11.9)**	
	***P* = 0.007**		***P* = 0.04**	
Mean percent change from baseline in VLDL-C				
at weeks 10 and 12, 95% CI*, %	–15.9	7.1	–22.9	5.0
	(–25.3, –6.5)	(–3.5, 17.6)	(–31.2, –14.5)	(–4.9, 14.8)
Difference*,**	**–23.0 (–33.1 to –12.8)**		**–27.8 (–36.6 to –19.0)**	
	***P* < 0.0001**		***P* < 0.0001**	
Percent change from baseline in VLDL-C at				
week 12, 95% CI*, %	–10.6	11.2	–14.0	1.7
	(–20.9, –0.2)	(–0.9, 23.3)	(–22.8, –5.3)	(–9.3, 12.8)
Difference*,**	**–21.8 (–34.3 to –9.3)**		**–15.7 (–26.3 to –5.2)**	
	***P* = 0.0008**		***P* = 0.004**	

*Least-squares mean is shown from the repeated measures linear effects model including treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit as covariates. **Treatment difference between the evolocumab and placebo groups is shown. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly; SC, subcutaneous; VLDL-C, very low-density lipoprotein cholesterol.

Table S3. Results of sensitivity analysis

Endpoint	Evolocumab 140 mg SC Q2W (N = 79)	Placebo SC Q2W (N = 41)	Evolocumab 420 mg SC QM (N = 80)	Placebo SC QM (N = 41)
Multiple imputation				
Mean percent change from baseline in LDL-C at weeks 10 and 12, 95% CI*, %	–60.8 (–69.5, –52.1)	–0.3 (–10.7, 10.2)	–68.0 (–75.8, –60.2)	–1.5 (–10.6, 7.6)
Difference*,**	**–60.5 (–70.9 to –50.2)** *P* < 0.0001		**–66.5 (–74.7 to –58.3)** *P* < 0.0001	
Percent change from baseline in LDL-C at week 12, 95% CI*, %	–61.2 (–70.9, –51.6)	–0.3 (–12.2, 11.7)	–61.6 (–69.6, –53.6)	1.5 (–8.2, 11.2)
Difference*,**	**–61.0 (–72.4 to –49.5)** *P* < 0.0001		**–63.1 (–72.0 to –54.1)** *P* < 0.0001	

*Least-squares mean is shown from the repeated measures linear effects model including treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit as covariates. **Treatment difference between the evolocumab and placebo groups are shown. CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly; SC, subcutaneous.

Reference

1. Y. Hochberg, A sharper Bonferroni procedure for multiple tests of significance, Biometrika 75 (1988) 800–802.