1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.2 全臨床試験一覧表							
5.2-1	全臨床試験一覧表						
5.3 臨床試験報告書							
5.3.1 生物薬剤学試験報告書							
5.3.1.1 バイオアベイラビリティ（BA）試験報告書							
5.3.1.1-1	Pharmacokinetic study on the drug-food interaction after a 10 mg single oral administration in 12 healthy young volunteers. Determination of the influence of time of administration on the steady state pharmacokinetic profile. Open, cross-over study. PKH-16257-003 (NP06817)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.1-2	Pharmacokinetic and pharmacodynamic modelling of the effects of S 16257-2 on resting and exercise heart rate in 18 healthy volunteers after a single, then repeated, administration of S 16257-2 by the oral route (10 and 20 mg base twice daily) (double blind parallel group study) and after a single administration of S 16257-2 by the intravenous route (10 mg base, bolus). Open study. PKH-16257-001 (NP07151) ※5.3.4.1-16と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.1-3	Combined population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of S16257 and its main active metabolite S18982 in healthy volunteers, following ivabradine administration coadministered or not with CYP 3A4 inhibitors. (NP27189) ※5.3.4.1-28と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.2 比較BA試験及び生物学的同等性（BE）試験報告書							
5.3.1.2-1	A combined analysis of S 16257-2 : pharmacokinetics after repeated oral dose twice a day in patients. Population pharmacokinetic analysis. (NP15388) ※5.3.3.2-1と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.3 *In Vitro -In Vivo* の関連を検討した試験報告書							
該当資料なし							
5.3.1.4 生物学的及び理化学的分析法検討報告書							

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.1.4-1	DETERMINATION OF ONO-1162 (IVABRADINE) AND ITS METABOLITE ONO-IN-306 IN HUMAN LI-HEPARINISED PLASMA SAMPLES FROM A PHASE I CLINICAL STUDY (PROTOCOL NO. ONO-1162-01) BY LC-MS/MS	[redacted]	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.1.4-2	VALIDATION OF AN ANALYTICAL METHOD FOR THE MEASUREMENT OF S 16257 AND ITS METABOLITE S 18982 IN HUMAN PLASMA BY LIQUID-CHROMATOGRAPHY WITH TANDEM MASS SPECTROMETRY DETECTION		20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.1.4-3	THE VALIDATION OF AN LC-MS-MS PROCEDURE FOR THE MEASUREMENT OF S 16257 AND SIX METABOLITES IN HUMAN PLASMA	TECNOLOGY SERVIER	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.4-4	VALIDATION OF THE CHROMATOGRAPHIC PROCEDURE FOR THE MEASUREMENT OF S 16257 AND S 18982 IN PLASMA (RAT, DOG, HUMAN) AND URINE (HUMAN) BY LIQUID CHROMATOGRAPHY WITH NATIVE FLUORESCENCE DETECTION	TECNOLOGY SERVIER	19[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.1.4-5	DETERMINATION OF S16257 AND ITS METABOLITE S 18982 IN RAT, DOG AND HUMAN PLASMA	[redacted]	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.4-6	DETERMINATION OF S16257 AND ITS METABOLITE S 18982 IN RAT, DOG AND HUMAN URINE		19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.4-7	CROSS-VALIDATION BETWEEN TWO LC-MS/MS SYSTEMS API 365 AND API 3000 FOR THE DETERMINATION OF ONO-1162 (IVABRADINE) AND ITS METABOLITE ONO-IN-306		20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.1.4-8	CROSS-VALIDATION BETWEEN TWO LC-MS/MS SYSTEMS API 365 AND API 3000 FOR THE DETERMINATION OF ONO-1162 (IVABRADINE) AND ITS METABOLITE ONO-IN-306		20[redacted]年[redacted]月	海外	海外	社内資料	評価

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.1.4-9	INTERLABORATORY COMPARISON OF TWO ANALYTICAL METHODS FOR THE QUANTITATIVE MEASUREMENT OF S 16257 AND S 18982 IN HUMAN PLASMA: LIQUID CHROMATOGRAPHY WITH FLUORESCENCE DETECTION AND LIQUID CHROMATOGRAPHY WITH MASS SPECTROMETRY DETECTION	TECNOLOGY SERVIER	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.4-10	INTERLABORATORY COMPARISON OF TWO ANALYTICAL METHODS FOR QUANTITATIVE MEASUREMENT OF S 16257 AND ITS METABOLITE S 18982 IN HUMAN PLASMA: LC-FLUORIMETRIC METHOD AND LC-MS-MS METHOD	TECNOLOGY SERVIER	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.4-11	SUMMARY OF PRECLINICAL BIOANALYTICS FOR DETERMINATION OF S 16257 AND ITS METABOLITE S 18982	TECNOLOGY SERVIER	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.1.4-12	DETERMINATION OF S 16257 IN PLASMA USING AUTOMATED LIQUID-SOLID EXTRACTION AND LIQUID CHROMATOGRAPHY WITH FLUORESCENCE DETECTION	TECNOLOGY SERVIER	19[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.1.4-13	VALIDATION OF AN ANALYTICAL METHOD FOR THE MEASUREMENT OF S 16257 AND ITS METABOLITE S 18982 IN HUMAN PLASMA BY LIQUID-CHROMATOGRAPHY WITH TANDEM MASS SPECTROMETRY DETECTION	[redacted]	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.1.4-14	STABILITY OF S 16257 AND ITS N-DEMETHYLATED METABOLITE (S 18982) IN HUMAN URINE	TECNOLOGY SERVIER	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書							
5.3.2.1 血漿蛋白結合試験報告書							
5.3.2.1-1	*Ex vivo* protein binding of S 16257 in healthy volunteers, in subjects with impaired hepatic function and in subjects with severe renal failure. (NP15217)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2 肝代謝及び薬物相互作用試験報告書							

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.2.2-1	Determination of the kinetic parameters (Km, Vmax) of the biotransformation of S 16257 and S 18982 and assessment of drug interaction with therapeutic agents which are substrates or inhibitors of CYP3A4 using human hepatic microsomes. (NP15218)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2-2	Investigation of the contribution of cytochrome 3A to the metabolism of [^{14}C]-S 16257. (NP29916)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2-3	Complementary assessment of drug-drug interaction by concomitant incubation of human hepatic microsomes with S 16257 and therapeutic agents which are substrates or inhibitors of CYP3A4. (NP25546)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2-4	Evaluation of induction properties of S 16257 on human CYP450 enzymatic activities: *in vitro* experiments. (NP32927)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2-5	Inhibitory properties of S 16257 on human CYP3A4. (NP08070)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2-6	Assessment of the inhibitory properties of S 16257 on human CYP2C18/19 and 2E1. (NP08471)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2-7	Complementary assessment of inhibitory properties of S 16257 on human cytochrome P450 using liver microsomes. (NP16016)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2-8	Interactions of S 16257 and S 18982 with hepatic transporters. (NP31384)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.2-9	*In vitro* interaction studies of S 16257 with P-gp (MDR1/ABCB1) and BCRP (ABCG2) in the vesicular transport assay and in bidirectional transport (Papp) studies on transfected MDCKII monolayers and with human OATP1B1 (OATP2, OATP-C), OATP1B3 (OATP8), OCT1, OCT2, OAT1 and OAT3 uptake transporters. (NP32566)	[redacted]	20[redacted]年[redacted]月	海外	海外	社内資料	評価

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.2.2-10	*In vitro* interaction studies of S 18982 with P-gp (MDR1/ABCB1) and BCRP (ABCG2) in the vesicular transport assay and in bidirectional transport (Papp) studies on transfected MDCKII monolayers and with human OATP1B1 (OATP2, OATP-C), OATP1B3 (OATP8) and OCT1 uptake transporters. (NP32565)	[redacted]	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.2.3 他のヒト生体試料を用いた試験報告書							
5.3.2.3-1	Investigation into the cellular transport of S 16257 and S 18982 using the Caco-2 cell line. (NP15184)	Technologie Servier	20[redacted]年[redacted]月	海外	海外	社内資料	評価
5.3.3 臨床薬物動態（PK）試験報告書							
5.3.3.1 健康被験者におけるPK及び初期忍容性試験報告書							
5.3.3.1-1	Excretion balance, pharmacokinetic and metabolism study after a single oral dose of 20 mg 14C-S 16257 in four healthy male volunteers. (Open study) PKH-16257-002 (NP06963)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.1-2	Evaluation of the concentration of ivabradine in semen following repeated administration of ivabradine (10 mg b.i.d.) in healthy volunteers. An open, monocenter, single-arm study in healthy volunteers. PKH-16257-013 (NP15084)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.1-3	Assessment of the safety and pharmacokinetics of increasing single oral doses and one single intravenous dose of S 18982 in healthy volunteers. A double-blind, randomized, placebo-controlled study. CL1-16257-039 (NP15148)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.1-4	First phase Ⅰ study of S16257 : Effects of increasing single oral doses on tolerance and pharmacokinetics in healthy volunteers. A double-bind,randomised,placebo-controlled, single rising dose study. (in 76 healthy volunteers, dose of S 16257 from 0.5 mg to 40 mg). CL1-16257-001 (NP06933) ※5.3.4.1-2と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.1-5	Effects of increasing repeated oral doses of S 16257 in comparison to placebo during 7 hospitalization days on tolerance and pharmacokinetics in 60 healthy volunteers. A double-blind, randomized, placebo-controlled, dose ranging study. CL1-16257-002 (NP06870) ※5.3.4.1-3と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.3.1-6	Effects of increasing intravenous bolus doses of S 16257-2 on tolerance and pharmacokinetics in 60 healthy volunteers. A double blind, randomised, placebo controlled, single rising dose study. CL1-16257-003 (NP06965) ※5.3.4.1-4と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.1-7	Effects of 48 hours intravenous infusion of increasing doses of S16257 (16 mg, 32 mg, 48 mg, 64 mg, 80 mg) on tolerance and pharmacokinetics in 50 healthy volunteers. A double-blind randomised, placebo controlled, dose ranging study. CL1-16257-004 (NP06871) ※5.3.4.1-5と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.2 患者におけるPK及び初期忍容性試験報告書							
5.3.3.2-1	A combined analysis of S 16257-2 : pharmacokinetics after repeated oral dose twice a day in patients. Population pharmacokinetic analysis. (NP15388)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.2-2	Dose ranging evaluation of the safety and efficacy of 4 single oral doses of S-16257-2 (5 mg - 10 mg - 15 mg - 20 mg) and placebo in 50 hospitalized patients with chronic stable angina pectoris. CL2-16257-006 (NP06869) ※5.3.5.4-2と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.2-3	Dose ranging evaluation of the antianginal efficacy and safety of three oral doses (2.5, 5, 10 mg bid) of S 16257 in comparison to placebo in 360 patients with stable effort angina pectoris. A 2-week multicentre, parallel group, double-blind, randomised placebo controlled trial. CL2-16257-009 (NP07495) ※5.3.5.4-3と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.3 内因性要因を検討したPK試験報告書							
5.3.3.3-1	Evaluation of the pharmacokinetics, tolerance, and safety of oral (5 mg) and intravenous (0.2 mg/kg) single administrations of ivabradine in patients with impaired hepatic function. An open-label, monocentre study. PKH-16257-008 (NP15305)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.3-2	Evaluation of the safety and pharmacokinetics of oral single administration of ivabradine (10 mg) in patients with severe renal failure. An open, monocentre, single-arm study. PKH-16257-015 (NP26945)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.3.3-3	Assessment of the effect of dialysis on the pharmacokinetics of S 16257 and S 18982 . (NP15364)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.3-4	Evaluation of the effects of a 3-month chronic oral administration of ivabradine 10 mg b.i.d versus placebo, in patients treated for stable congestive heart failure and with a history of coronary heartery disease. CL2-16257-030 (NP15440) ※5.3.5.1-3と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.3-5	Pharmacokinetic and Analytical report - Evaluation of the effects of 3 successive oral dosages (2.5; 5; 7.5 mg b.i.d.) of ivabradine in patients with stable moderate to severe systolic chronic heart failure treated with beta-blockers. A 9 weeks pilot, open labelled, international multicenter study. CL2-16257-062 (NP27503) ※5.3.5.2-3と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.3-6	Pharmacokinetic sub-study to the clinical study CL3-16257-063 (SHIFT). Effects of Ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction . A three-year randomised, double-blind, placebo-controlled international multicentre study. (NP30429) ※5.3.5.1-8と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.3-7	A combined analysis of S 16257-2 : pharmacokinetics after repeated oral dose twice a day in patients. Population pharmacokinetic analysis. (NP15388) ※5.3.3.2-1と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 外因性要因を検討したPK試験報告書							
5.3.3.4 -1	Evaluation of the tolerance, safety and pharmacokinetics of steady state oral co-administrations of ivabradine 10 mg b.i.d. and simvastatine 20 mg o.d. in healthy volunteers. CL1-16257-042 (NP08326)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -2	Evaluation of the effects of a repeated oral co-administration of ivabradine 10 mg b.i.d. with lacidipine 4 mg o.d. in healthy volunteers. A randomised, double blind, monocentre, cross-over study. CL1-16257-048 (NP15296)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.3.4 -3	Study of the influence of repeated administration of ketoconazole (200 mg p.o. during 5 days) on the pharmacodynamics and pharmacokinetics of S 16257 and its metabolites after single administration of S 16257-2 (10 mg p.o.) in twelve healthy male volunteers. (Open study) PKH-16257-004 (NP08145)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -4	Effect of repeated administration of josamycin on the safety and pharmacokinetics of S 16257 (single oral administration of 10 mg) in 12 young healthy volunteers. (Open-monocentric study) PKH-16257-005 (NP08139)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -5	Study of the effect of repeated administration of ketoconazole (200 mg po for 5 days) on the pharmacokinetics and safety of S 16257 and its metabolite following single administration of S 16257-2 (10 mg po) in 12 healthy female volunteers. (single center – open study) PKH-16257-006 (NP08141)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -6	Effect of repeated administrations of grapefruit juice on the safety and pharmacokinetics of S 16257 and S 18982 (active metabolite) when co-administered with ivabradine 10 mg in healthy male volunteers. An open, monocenter study. PKH-16257-007 (NP08231)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -7	Evaluation of the effect of omeprazole (40 mg o.d.) and lansoprazole (60 mg o.d.), both in repeated oral administration, on the pharmacokinetics of ivabradine administered orally (10 mg o.d.) in healthy volunteers. A randomized, cross-over, open, mnocenter study. PKH-16257-009 (NP15099)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -8	Evaluation of the effect of the combination of ketoconazole and ivabradine (S 16257-2) or its metabolite (S 18982) following single oral and single intravenous administration of S 16257-2 or S 18982 in 2 groups of 6 healthy male volunteers. An open, monocentre, two independent single arms study. PKH-16257-010 (NP15382)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.3.4 -9	Evaluation of the effects of the dose adaptation of ivabradine repeated oral administration from 10 mg b.i.d. alone to escalating doses of 2.5 mg b.i.d., 5 mg b.i.d. and 10 mg b.i.d. when co-administered with ketoconazole 200 mg o.d. in healthy volunteers. An open, single arm, monocentre study. PKH-16257-012 (NP15383)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -10	Evaluation of the effects of repeated oral administration of Hypericum perforatum (300 mg t.i.d.) on the pharmacokinetics and safety of S 16257 and its metabolite following oral administration of S 16257 (10 mg) in healthy subjects. An open, two-periods, cross-over, non-randomised, Phase I, pharmacokinetic interaction monocentre study. PKH-16257-014 (NP15304)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -11	Effect of a repeated oral administration of ivabradine (10 mg b.i.d. for 6 days) on the pharmacokinetics of metformin following single oral administration of metformin (500 mg) in healthy volunteers. A monocentre, open label study. PKH-16257-105	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -12	Evaluation of the tolerance, safety and pharmacokinetics of oral repeated administrations of ivabradine 10 mg b.i.d. when co-administered with diltiazem 120 mg b.i.d. in healthy volunteers. An open, monocentre study. CL1-16257-027 (NP15102) ※5.3.4.1-9と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -13	Evaluation of the tolerance, safety and pharmacokinetics of oral repeated administrations of ivabradine 10 mg b.i.d. when co-administered with verapamil 120 mg b.i.d. in healthy volunteers. An open, monocenter study. CL1-16257-029 (NP15041) ※5.3.4.1-10と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -14	Evaluation of the tolerance, safety and pharmacokinetics of oral ivabradine (10 mg b.i.d.) and warfarin co-administered in healthy volunteers. An open-label, monocenter study. CL1-16257-033 (NP08316) ※5.3.4.1-11と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.3.4 -15	Evaluation of the effects of a repeated oral administration of ivabradine 10 mg b.i.d. when co-administered with digoxin 0.375 mg o.d. in healthy volunteers. CL1-16257-036 (NP08235) ※5.3.4.1-12と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -16	Evaluation of the effects of a repeated oral co-administration of ivabradine 10 mg b.i.d. with atenolol 50 mg o.d. in healthy volunteers. An open, monocentre study. CL1-16257-043 (NP15306) ※5.3.4.1-14と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -17	Evaluation of the effects of a repeated oral co-administration of ivabradine 10 mg b.i.d. with atenolol 50 mg o.d. in patients with stable coronary artery disease. CL2-16257-026 (NP15313) ※5.3.4.2-1と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -18	Evaluation of the effects of a repeated oral co-administration of ivabradine (escalating doses of 2.5 and 5 mg b.i.d.) when co-administered with diltiazem (slow-release, 120 mg b.i.d.) to patients with stable coronary artery disease. CL2-16257-028 (NP15389) ※5.3.4.2-2と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -19	Evaluation of the effects of a repeated oral administration of ivabradine 10 mg b.i.d. when co-administered to patients treated with amiodarone 200 mg o.d. CL2-16257-050 (NP15381) ※5.3.4.2-3と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -20	Evaluation of the effects of a repeated oral co-administration of ivabradine 10 mg b.i.d. with sildenafil (single doses of 50 and 100 mg o.d.) in patients with stable coronoray artery disease. CL2-16257-054 (NP15371) ※5.3.4.2-4と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.4 -21	Effect of a repeated oral administration of ivabradine (10 mg b.i.d. for 6 days) on the pharmacokinetics of metformin following single oral administration of metformin (500 mg) in healthy volunteers. A monocentre, open label study. PKH-16257-105 PHARMACOKINETIC REPORT	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.5 ポピュレーションPK試験報告書							

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.3.5-1	Combined-analysis: ivabradine (S 16257) and its main metabolite (S 18982) pharmacokinetics after single and repeated oral dose twice a day in healthy volunteers under fasting and fed conditions (NP08547)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.5-2	A combined analysis of S 16257-2 : pharmacokinetics after repeated oral dose twice a day in patients. Population pharmacokinetic analysis. (NP15388) ※5.3.3.2-1と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.5-3	Meta-analysis of S-16257-2 : Pharmacokinetics /pharmacodynamics after single intravenous bolus, single oral dose and repeated oral dose twice a day in healthy volunteers (NP06695) ※5.3.4.1-26と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.3.5-4	Combined population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of S16257 and its main active metabolite S18982 in healthy volunteers, following ivabradine administration coadministered or not with CYP 3A4 inhibitors (NP27189) ※5.3.4.1-28と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4 臨床薬力学（PD）試験報告書							
5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書							
5.3.4.1-1	ONO-1162 第Ⅰ相試験 単回及び反復経口投与試験（ONO-1162-01）	小野薬品工業株式会社	20[redacted]年[redacted]月	国内	国内	社内資料	評価
5.3.4.1-2	First phase I study of S16257 : Effects of increasing single oral doses on tolerance and pharmacokinetics in healthy volunteers. A double-bind,randomised,placebo-controlled, single rising dose study. (in 76 healthy volunteers, dose of S 16257 from 0.5 mg to 40 mg). CL1-16257-001 (NP06933)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-3	Effects of increasing repeated oral doses of S 16257 in comparison to placebo during 7 hospitalization days on tolerance and pharmacokinetics in 60 healthy volunteers. A double-blind, randomized, placebo-controlled, dose ranging study. CL1-16257-002 (NP06870)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-4	Effects of increasing intravenous bolus doses of S 16257-2 on tolerance and pharmacokinetics in 60 healthy volunteers. A double blind, randomised, placebo controlled, single rising dose study (1, 2, 4, 8, 16, 24 mg). CL1-16257-003 (NP06965)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.4.1-5	Effects of 48 hours intravenous infusion of increasing doses of S16257 (16 mg, 32 mg, 48 mg, 64 mg, 80 mg) on tolerance and pharmacokinetics in 50 healthy volunteers. A double-blind randomised, placebo-controlled, dose ranging study. CL1-16257-004 (NP06871)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-6	Study of the electrophysiological effects of S 16257-2 in 12 healthy volunteers using quantitative electrocardiography. Single oral administration of 3 doses of S 16257 (10, 20 and 30 mg) and placebo. Double-blind – Latin square. CL1-16257-007 (NP15365)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-7	Comparison of the haemodynamic and biologic effects of single oral doses of S 16257-2 (30 mg), propranolol (40 mg) and placebo in 9 healthy volunteers. A double-blind, randomized latin square study. CL1-16257-008 (NP07299)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-8	Evaluation of the effects of a repeated administration of ivabradine 10 mg b.i.d. on platelet function in healthy volunteers treated with a single administration of aspirin 100 mg. CL1-16257-024 (NP08159)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-9	Evaluation of the tolerance, safety and pharmacokinetics of oral repeated administrations of ivabradine 10 mg b.i.d. when co-administered with diltiazem 120 mg b.i.d. in healthy volunteers. An open, monocentre study. CL1-16257-027 (NP15102)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-10	Evaluation of the tolerance, safety and pharmacokinetics of oral repeated administrations of ivabradine 10 mg b.i.d. when co-administered with verapamil 120 mg b.i.d. in healthy volunteers. An open, monocenter study. CL1-16257-029 (NP15041)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-11	Evaluation of the tolerance, safety and pharmacokinetics of oral ivabradine (10 mg b.i.d.) and warfarin co-administered in healthy volunteers. An open-label, monocenter study. CL1-16257-033 (NP08316)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.4.1-12	Evaluation of the effects of a repeated oral administration of ivabradine 10 mg b.i.d. when co-administered with digoxin 0.375 mg o.d. in healthy volunteers. CL1-16257-036 (NP08235)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-13	Evaluation of the effects of a repeated administration of ivabradine 10 mg b.i.d. on platelet function in healthy volunteers treated with a repeated administration of asprin 75 mg o.d. A randomized, cross-over, open, single center study. CL1-16257-041 (NP08331)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-14	Evaluation of the effects of a repeated oral co-administration of ivabradine 10 mg b.i.d. with atenolol 50 mg o.d. in healthy volunteers. An open, monocentre study. CL1-16257-043 (NP15306)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-15	Evaluation of the effects of a repeated oral administration of ivabradine 10 mg b.i.d. when co-administered with a single oral dose of imipramine 100 mg or thioridazine 50 mg in healthy volunteers. An open monocenter study, with two independent single arms. CL1-16257-049 (NP15096)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-16	Pharmacokinetic and pharmacodynamic modelling of the effects of S 16257-2 on resting and exercise heart rate in 18 healthy volunteers after a single, then repeated, administration of S 16257-2 by the oral route (10 and 20 mg base twice daily) (double blind parallel group study) and after a single administration of S 16257-2 by the intravenous route (10 mg base, bolus). (Open study) PKH-16257-001 (NP07151)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-17	Electrophysiologic effects of a single intravenous administration of S 16257 (0.2 - 0.3 mg/kg) in adult patients with normal baseline electrophysiologic examination. CL2-16257-010 (NP07862)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.4.1-18	Effects of a single S 16257 intravenous administration (up to 0.25 mg/kg) on global indices of left ventricular function in 44 patients with abnormal left ventricular function. - Single-blind placebo-controlled Phase II study - CL2-16257-011 (NP07864)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-19	Single intravenous administration of S 16257 (0.20 mg/kg) for the treatment of atrial fibrillation following cardiac surgery: randomised, single-blind, placebo controlled study in 52 adult patients. CL2-16257-012 (NP08595)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-20	S 16257 for the treatment of paroxysmal atrial fibrillation: a multicenter, randomised, double-blind, crossover study of S 16257 (5 – 10 mg bid) and placebo. CL2-16257-013 (NP15224)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-21	Electrophysiological effects of a single intravenous administration of S 16257 (0.2 mg/kg) in adult patients with normal baseline electrophysiological examination - Open study - CL2-16257-014 (NP07778)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-22	Electrophysiologic effects of a single intravenous administration of S 16257-2 (0.2 - 0.3 mg/kg) in 16 adult patients with normal and near-normal baseline electrophysiologic examination. Open study. CL2-16257-015 (NP15284)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-23	Effects of a single intravenous administration of ivabradine (0.20 mg/kg) on the electrophysiologic parameters in adult patients with abnormalities of atrioventricular and/or ventricular conduction. CL2-16257-045 (NP27781)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-24	A non-invasive electrophysiological study of ivabradine (the NESI study). A double blind, randomised, placebo-controlled, single centre study. CL2-16257-052 (NP28221)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-25	Evaluation of the effects on peripheral and central haemodynamics parameters, safety, and tolerance of 3-hour intravenous perfusion (0.1 mg/kg) of ivabradine given to severe congestive heart failure patients. A pilot, open labelled, monocenter study. CL2-16257-053 (NP24159)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.4.1-26	Meta-analysis of S-16257-2 : Pharmacokinetics /pharmacodynamics after single intravenous bolus, single oral dose and repeated oral dose twice a day in healthy volunteers. (NP06695)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-27	Evaluation of the fed condition on heart rate after an oral administration of 10 mg b.i.d. of S 16257. (A simulation analysis) (NP15386)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-28	Combined population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of S16257 and its main active metabolite S18982 in healthy volunteers, following ivabradine administration co-administered or not with CYP 3A4 inhibitors. (NP27189)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-29	Evaluation of the tolerance, safety and pharmacokinetics of steady state oral co-administrations of ivabradine 10 mg b.i.d. and simvastatine 20 mg o.d. in healthy volunteers. CL1-16257-042 (NP08326) ※5.3.3.4-1と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-30	Evaluation of the effects of a repeated oral co-administration of ivabradine 10 mg b.i.d. with lacidipine 4 mg o.d. in healthy volunteers. A randomised, double blind, monocentre, cross-over study. CL1-16257-048 (NP15296) ※5.3.3.4-2と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-31	Study of the influence of repeated administration of ketoconazole (200 mg p.o. during 5 days) on the pharmacodynamics and pharmacokinetics of S 16257 and its metabolites after single administration of S 16257-2 (10 mg p.o.) in twelve healthy male volunteers. PKH-16257-004 (NP08145) ※5.3.3.4-3と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-32	Effects of repeated administration of josamycin on the safety and pharmacokinetics of S 16257 (single oral administration of 10 mg) in 12 young healthy volunteers (open-monocentric study) PKH-16257-005 (NP08139) ※5.3.3.4-4と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.4.1-33	Study of the effect of repeated administration of ketoconazole (200 mg po for 5 days) on the pharmacokinetics and safety of S 16257 and its metabolite following single administration of S 16257-2 (10 mg po) in 12 healthy female volunteers. (single center – open study) PKH-16257-006 (NP08141) ※5.3.3.4-5と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-34	Evaluation of the effects of the dose adaptation of ivabradine repeated oral administration from 10 mg b.i.d. alone to escalating doses of 2.5 mg b.i.d., 5 mg b.i.d. and 10 mg b.i.d. when co-administered with ketoconazole 200 mg o.d. in healthy volunteers. An open, single arm, monocentre study. PKH-16257-010 (NP15382) ※5.3.3.4-8と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-35	Evaluation of the effects of the dose adaptation of ivabradine repeated oral administration from 10 mg b.i.d. alone to escalating doses of 2.5 mg b.i.d., 5 mg b.i.d. and 10 mg b.i.d. when co-administered with ketoconazole 200 mg o.d. in healthy volunteers. An open, single arm, monocentre study. PKH-16257-012 (NP15383) ※5.3.3.4-9と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.1-36	Evaluation of the effects of repeated oral administration of Hypericum perforatum (300 mg t.i.d.) on the pharmacokinetics and safety of S 16257 and its metabolite following oral administration of S 16257 (10 mg) in healthy subjects. An open, two-periods, cross-over, non-randomised, Phase I, pharmacokinetic interaction monocentre study. PKH-16257-014 (NP15304) ※5.3.3.4-10と同資料	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.2 患者におけるPD試験及びPK/PD試験報告書							
5.3.4.2-1	Evaluation of the effects of a repeated oral co-administration of ivabradine 10 mg b.i.d. with atenolol 50 mg o.d. in patients with stable coronary artery disease. An open, monocentre study. CL2-16257-026 (NP15313)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.4.2-2	Evaluation of the effects of a repeated oral co-administration of ivabradine (escalating doses of 2.5 and 5 mg b.i.d.) when co-administered with diltiazem (slow-release, 120 mg b.i.d.) to patients with stable coronary artery disease. A double-blind, randomised, placebo-controlled, 2 arms parallel groups study, in 2 centres. CL2-16257-028 (NP15389)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.2-3	Evaluation of the effects of a repeated oral administration of ivabradine 10 mg b.i.d. when co-administered to patients treated with amiodarone 200 mg o.d. An open, single arm study in two centres. CL2-16257-050 (NP15381)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.2-4	Evaluation of the effects of a repeated oral co-administration of ivabradine 10 mg b.i.d. with sildenafil (single doses of 50 and 100 mg o.d.) in patients with stable coronoray artery disease. An open, monocentre study. CL2-16257-054 (NP15371)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.2-5	Combined-analysis of S 16257-2: pharmacokinetic and pharmacodynamic modelling of the S 16257 and S 18982 concentration effects on heart rate after repeated oral dose twice a day in patients. (NP15444)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.2-6	Assessment of the QTc interval prolongation potential of S 16257-2 after oral administration in healthy volunteers and patients by using a pooled studies heart rate correction formula. Combined analysis (NP15442)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.2-7	Dose ranging evaluation of the safety and efficacy of 4 single oral doses of S-16257-2 (5 mg - 10 mg - 15 mg - 20 mg) and placebo in 50 hospitalized patients with chronic stable angina pectoris. CL2-16257-006 (NP06869) ※5.3.5.4-2と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.4.2-8	Dose ranging evaluation of the antianginal efficacy and safety of three oral doses (2.5, 5, 10 mg bid) of S 16257 in comparison to placebo in 360 patients with stable effort angina pectoris. A 2-week multicentre, parallel group, double-blind, randomised placebo controlled trial. CL2-16257-009 (NP07495) ※5.3.5.4-3と同資料	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.4.2-9	Long-term effect of S 16257 and S 18982 concentrations on heart rate after repeated oral doses of S 16257 twice a day in patients, at rest, in supine or standing position, or during exercise tolerance tests. (NP32761)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5 有効性及び安全性試験報告書							
5.3.5.1 申請する適応症に関する比較対照試験報告書							
5.3.5.1-1	ONO-1162第Ⅱ相試験 慢性心不全に対するプラセボを対照とした多施設共同二重盲検無作為化並行群間比較試験（ONO-1162-02）	小野薬品工業株式会社	2015年[redacted]月	国内	国内	社内資料	評価
5.3.5.1-2	ONO-1162 第Ⅲ相試験 慢性心不全に対するプラセボを対照とした多施設共同二重盲検無作為化並行群間比較試験（ONO-1162-03）	小野薬品工業株式会社	2018年[redacted]月	国内	国内	社内資料	評価
5.3.5.1-3	Evaluation of the effects of a 3-month chronic oral administration of ivabradine 10 mg b.i.d versus placebo, in patients treated for stable congestive heart failure and with a history of coronary artery disease. A double-blind, randomised, parallel group, placebo-controlled, multicentre study. CL2-16257-030 (NP15440)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.1-4	Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction: SHIFT study. A three-year randomised double-blind placebo-controlled international multicentre study. CL3-16257-063 (NP29800)	Les Laboratoires Servier	2010年10月	海外	海外	社内資料	評価

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.5.1-5	Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study. HOLTER ECG SUB-STUDY to the clinical study. CL3-16257-063 (NP30215)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.1-6	Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study. Echocardiography / NT-proBNP sub-study protocol associated to the clinical protocol No. CL3-16257-063, Systolic Heart Failure treatment with the If inhibitor ivabradine Trial (SHIFT). (NP30294)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.1-7	Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study. Patient-reported outcomes sub-study to the clinical study CL3-16257-063. (NP30324)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.1-8	Pharmacokinetic sub-study to the clinical study CL3-16257-063. Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction . A three-year randomised, double-blind, placebo-controlled international multicentre study. (NP30429)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.2 非対照試験報告書							
5.3.5.2-1	Evaluation of the effects of ivabradine taken orally for 24 weeks in patients with symptomatic chronic heart failure. Open, multicentre pilot study. CL2-16257-061 (NP28337)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.5.2-2	Evaluation of the effects of 3 successive oral dosages (2.5; 5; 7.5 mg b.i.d.) of ivabradine in patients with stable moderate to severe systolic chronic heart failure treated with beta-blockers. A 9-week pilot, open-label, international multicenter study. CL2-16257-062 (NP26408)	Les Laboratoires Servier	2008年5月	海外	海外	社内資料	参考
5.3.5.2-3	Evaluation of the effects of 3 successive oral dosages (2.5; 5; 7.5 mg b.i.d.) of ivabradine in patients with stable moderate to severe systolic chronic heart failure treated with beta-blockers. A 9-week pilot, open-label, international multicenter study. CL2-16257-062 (NP27503)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.3 複数の試験成績を併せて解析した報告書							
5.3.5.3-1	Additional post-hoc analyses - Efficacy (NP32845)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.3-2	Additional post-hoc analyses - Safety (NP32844)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.3-3	健康成人及び慢性心不全患者を対象とした国内及び海外臨床試験の成績を利用したONO-1162 の薬物動態の民族差比較	小野薬品工業株式会社	20[redacted]年[redacted]月	国内	国内	社内資料	参考
5.3.5.3-4	国内試験事後解析結果	小野薬品工業株式会社	20[redacted]年[redacted]月	国内	国内	社内資料	参考
5.3.5.4 その他の臨床試験報告書							
5.3.5.4-1	Effects of ivabradine on driving performance in healthy volunteers after repeated oral administration inducing or not visual symptoms. CL1-16257-055 (NP15373)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.4-2	Dose ranging evaluation of the safety and efficacy of 4 single oral doses of S-16257-2 (5 mg - 10 mg - 15 mg - 20 mg) and placebo in 50 hospitalized patients with chronic stable angina pectoris. CL2-16257-006 (NP06869)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.4-3	Dose ranging evaluation of the antianginal efficacy and safety of three oral doses (2.5, 5, 10 mg bid) of S 16257 in comparison to placebo in 360 patients with stable effort angina pectoris. A 2-week multicentre, parallel group, double-blind, randomised placebo controlled trial. CL2-16257-009 (NP07495)	Les Laboratoires Servier	19[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.5.4-4	Evaluation of the overall and cardiac safety and pharmacokinetics of rising oral doses of ivabradine (10 mg, 15 mg, 20 mg b.i.d.) versus atenolol (50 mg o.d.) in patients with proven coronary artery disease. An international four-week, multicentric, parallel group, double-blind, randomised, controlled study. CL2-16257-047 (NP15429)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.4-5	Evaluation of the anti-anginal efficacy and safety of oral chronic administration of ivabradine (5 mg b.i.d. then 7.5 mg b.i.d. or 10 mg b.i.d.) compared to atenolol (50 mg o.d. then 100 mg o.d.), in patients with stable effort angina pectoris. A 4-month international multicentre, parallel group, double blind, randomised, controlled trial. CL3-16257-017 (NP15194)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.4-6	Evaluation of the antianginal efficacy and safety of oral chronic administration of ivabradine (5 mg b.i.d. or 7.5 mg b.i.d.) versus placebo in association to background therapy with amlodipine (10 mg o.d.) in patients with stable effort angina pectoris. A 3-month international multicentre, parallel group, double-blind, randomised, controlled trial. CL3-16257-018 (NP15344)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.4-7	Evaluation of the tolerance and safety of oral chronic administration of ivabradine 10 mg b.i.d. compared to atenolol 100 mg o.d. in 225 patients with stable effort angina pectoris. A 1-year, randomised, double-blind, controlled, parallel group, international multicentre trial. CL3-16257-019 (NP15390)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.4-8	Evaluation of the tolerance and safety of oral chronic administration of ivabradine (5 mg b.i.d. versus 7.5 mg b.i.d.) in 300 patients with stable effort angina pectoris. A 1-year international multicentre, parallel group, double-blind, randomised trial. CL3-16257-021 (NP15331)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.3.5.4-9	Evaluation of the anti-anginal efficacy and safety of oral chronic administration of ivabradine (7.5 mg b.i.d. or 10 mg b.i.d.) compared to amlodipine (10 mg o.d.), in patients with stable effort angina pectoris. A 3-month randomised double blind controlled, parallel-group, international, multicentre trial. CL3-16257-023 (NP15384)	Les Laboratoires Servier	20[redacted]年[redacted]月	海外	海外	社内資料	参考
5.3.5.4-10	Long-term (3 years) ophthalmic safety and cardiac efficacy and safety of ivabradine administered orally at the therapeutic doses (2.5/5/7.5 mg b.i.d.) on top of anti-anginal background therapy, to patients with chronic stable angina pectoris. An international, double blind-placebo controlled study. CL3-16257-067	Les Laboratoires Servier	2015年[redacted]月	海外	海外	社内資料	参考
5.3.5.4-11	Effect of ivabradine versus placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with chronic heart failure with preserved left ventricular ejection fraction. An 8-month, randomised double-blind, placebo controlled international, multicentre study. (EDIFY study) CL2-16257-101	Les Laboratoires Servier	2016年[redacted]月	海外	海外	社内資料	参考
5.3.6 市販後の使用経験に関する報告書							
5.3.6-1	16th Periodic Benefit-Risk Evaluation Report	Les Laboratoires Servier	2018年6月27日	海外	海外	社内資料	－
5.3.6-2	市販後に報告された有害事象の集計一覧（海外）	Les Laboratoires Servier	2018年6月27日	海外	国内	社内資料	－
5.3.6-3	Risk Management Plan ver 6	Les Laboratoires Servier	2017年12月6日	海外	国内	社内資料	－
5.3.7 患者データ一覧表及び症例記録							
5.3.7-1	患者データ一覧表	－	－	－	－	－	－
5.3.7-2	副作用一覧表	－	－	－	－	－	－
5.3.7-3	重篤な有害事象一覧表	－	－	－	－	－	－
5.3.7-4	臨床検査値異常変動一覧表	－	－	－	－	－	－
5.3.7-5	臨床検査値変動図	－	－	－	－	－	－
5.4 参考文献							
5.4-1	2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.	Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al.	－	－	－	Circulation. 2013; 128: e240-327.	－

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.4-2	2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC); Developed with the special contribution of the Heart Failure Association (HFA) of the ESC.	Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.	—	—	—	Eur Heart J. 2016; 37: 2129-200.	—
5.4-3	2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America.	Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al.	—	—	—	Circulation. 2017; 136: e137-61.	—
5.4-4	Analysis of chronic heart failure registry in the Tohoku district: third year follow-up.	Shiba N, Watanabe J, Shinozaki T, Koseki Y, Sakuma M, Kagaya Y, et al.	—	—	—	Circ J. 2004; 68: 427-34.	—
5.4-5	Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy.	Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, et al.	—	—	—	Lancet. 1993; 342: 1441-6.	—
5.4-6	Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD).	Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, Yokoshiki H, et al.	—	—	—	Circ J. 2009; 73: 1893-900. Erratum in: Circ J. 2009; 73: 2365.	—
5.4-7	Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry.	Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al.	—	—	—	J Am Coll Cardiol. 2007; 50: 768-77.	—
5.4-8	Clinical characteristics and outcome of hospitalized patients with heart failure in Japan.	Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Takeshita A.	—	—	—	Circ J. 2006; 70: 1617-23.	—

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.4-9	Note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure.	CPMP/EWP	—	—	—	CPMP/EWP/235/95, Rev. 1. December 1999.	—
5.4-10	EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot).	Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, et al.	—	—	—	Eur J Heart Fail. 2013; 15: 808-17.	—
5.4-11	EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population.	Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al.	—	—	—	Eur Heart J. 2006; 27: 2725-36.	—
5.4-12	Guidelines for the diagnosis and treatment of chronic heart failure: exective summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology.	Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al.	—	—	—	Eur Heart J. 2005; 26: 1115-40.	—
5.4-13	Heart rate and cardiovascular mortality: the Framingham Study.	Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA.	—	—	—	Am Heart J. 1987; 113: 1489-94	—
5.4-14	Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial.	Boehm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al.	—	—	—	Lancet. 2010; 376: 886-94.	—
5.4-15	Hormones and hemodynamics in heart failure.	Schrier RW, Abraham WT.	—	—	—	N Engl J Med. 1999; 341: 577-85.	—
5.4-16	I_f inhibition in cardiovascular diseases.	Thollon C, Vilaine JP.	—	—	—	Adv Pharmacol. 2010; 59: 53-92.	—
5.4-17	Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil-SR/trandolapril STudy (INVEST).	Kolloch R, Legler UF, Champion A, Cooper-Dehoff RM, Handberg E, Zhou Q, et al.	—	—	—	Eur Heart J. 2008; 29: 1327-34.	—

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.4-18	Impending epidemic: future projection of heart failure in Japan to the year 2055.	Okura Y, Ramadan MM, Ohno Y, Mitsuma W, Tanaka K, Ito M,et al.	―	―	―	Circ J. 2008; 72: 489-91.	―
5.4-19	Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people.	Jhund PS, MacIntyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, et al.	―	―	―	Circulation. 2009; 119: 515-23.	―
5.4-20	Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure.	McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW.	―	―	―	Ann Intern Med. 2009; 150: 784-94.	―
5.4-21	Outcomes, health policy, and managed care: Relationships between patient-reported outcome measures and clinical measures in outpatients with heart failure.	Flynn KE, Lin L, Ellis SJ, Russell SD, Spertus JA, Whellan DJ, et al.	―	―	―	Am Heart J. 2009; 158(4 suppl): S64-S71.	―
5.4-22	Outcome of heart failure with preserved ejection fraction in a population-based study.	Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al.	―	―	―	N Engl J Med. 2006; 355: 260-9.	―
5.4-23	Predictors of mortality and morbidity in patients with chronic heart failure.	Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJV, Swedberg KB, et al.	―	―	―	Eur Heart J. 2006; 27: 65-75.	―
5.4-24	Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute.	Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al.	―	―	―	Circulation. 2009; 119: 3070-7.	―
5.4-25	Survival after the onset of congestive heart failure in Framingham Heart Study subjects.	Ho KKL, Anderson KM, Kannel WB, Grossman W, Levy D.	―	―	―	Circulation. 1993; 88: 107-15.	―
5.4-26	Temporal trends in clinical characteristics, management and prognosis of patients with symptomatic heart failure in Japan: report from the CHART Studies.	Ushigome R, Sakata Y, Nochioka K, Miyata S, Miura M, Tadaki S, et al.	―	―	―	Circ J. 2015; 79: 2396-407.	―
5.4-27	The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial.	CIBIS-II investigators and committees.	―	―	―	Lancet. 1999; 353 : 9-13	―

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.4-28	The effect of carvedilol on morbidity and mortality in patients with chronic heart failure.	Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al.	－	－	－	N Engl J Med. 1996; 334: 1349-55.	－
5.4-29	Treatment of chronic heart failure with carvedilol in daily practice: the SATELLITE survey experience.	Lainscak M, Moullet C, Schoen N, Tendera M.	－	－	－	Int J Cardiol. 2007; 122: 149-55.	－
5.4-30	Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan: first report from the CHART-2 study.	Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H.	－	－	－	Circ J. 2011; 75: 823-33.	－
5.4-31	Trends in long-term cardiovascular mortality and morbidity in men and women with heart failure of ischemic versus non-ischemic aetiology in Western Australia between 1990 and 2005.	Teng THK, Hung J, Knuiman M, Stewart S, Arnolda L, Jacobs I, et al.	－	－	－	Int J Cardiol. 2012; 158: 405-10.	－
5.4-32	Trends in prevalence and outcome of heart failure with preserved ejection fraction.	Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM.	－	－	－	N Engl J Med. 2006; 355: 251-9.	－
5.4-33	急性・慢性心不全診療ガイドライン（2017年改訂版）	日本循環器学会／日本心不全学会	－	－	－	http://www.j-circ.or.jp/guideline/pdf/JCS2017_tsutsui_h.pdf（2018年10月閲覧）	－
5.4-34	抗心不全薬の臨床評価方法に関するガイドライン	厚生労働省	－	－	－	薬食審査発0329第18号，平成23年3月29日	－

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.4-35	循環器疾患診療実態調査報告書(2017年度実施・公表).	日本循環器学会.	－	－	－	http://www.j-circ.or.jp/jittai_chosa/jittai_chosa2016web.pdf（2018年10月閲覧）	－
5.4-36	脳卒中、心臓病その他の循環器病に係る診療提供体制の在り方に関する検討会. 脳卒中、心臓病その他の循環器病に係る診療提供体制の在り方について(平成29年7月)	厚生労働省	－	－	－	http://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000173149.pdf（2018年10月閲覧）	－
5.4-37	平成29年(2017)人口動態統計(確定数)の概況.	厚生労働省.	－	－	－	https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei17/dl/00_all.pdf（2018年10月閲覧）	－

1.12 添付資料一覧
イバブラジン塩酸塩

添付資料番号	タイトル	著者	試験実施期間（資料作成年月）	試験実施場所	報種類(国内，海外)	掲載紙	評価／参考
5.4-38	慢性心不全治療ガイドライン（2010年改訂版）	日本循環器学会	－	－	－	http://www.j-circ.or.jp/guideline/pdf/JCS2010_matsuzaki_h.pdf（2018年10月閲覧）	－