Title: Specified Drug-Use Survey (“Long-Term Use Survey”) on Zacras Combination Tablets LD & HD

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Note; This document was translated into English as the language on original version was Japanese.

Statistical Analysis Plan

Specified Drug-Use Survey (“Long-Term Use Survey”) on Zacras Combination Tablets LD & HD

PPD

Takeda Pharmaceutical Company Limited

PPD

3rd edition prepared on 29 November 2017

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1.0 Definitions of Terms, etc. and Handling of Test/Measurement Data

1.1 Definitions

Term	Definition
Zacras	Zacras Combination Tablets are abbreviated as Zacras in this document.
SOC	System organ class listed in the MedDRA/J
HLGT	High level group term listed in the MedDRA/J
PT	Preferred term listed in the MedDRA/J
LLT	Lowest level term listed in the MedDRA/J
Enrolled patient	Patient allowed to be enrolled
Patient from whom the CRF is collected	Patient from whom the CRF has been obtained
Patient from whom the CRF is not collected	Enrolled patient from whom the CRF has not been collected
Finalized patient	Patient from whom the CRF is collected who has the date of CRF completion entered into the PMS system or who requires no information on the CRF status and has not been excluded from the survey
Non-finalized patient	Patient from whom the CRF is collected who has not been finalized
Patient included in safety evaluation	Finalized patient who is included in safety evaluation
Patient excluded from safety evaluation	Finalized patient who is excluded from safety evaluation
Patient included in efficacy evaluation	Patient included in safety evaluation who is included in efficacy evaluation
Patient excluded from efficacy evaluation	Patient included in safety evaluation who is excluded from safety evaluation
Presence or absence of change in daily dose of Zacras	"Yes" for patients with a change in daily dose between the start of treatment with Zacras and the final assessment
Duration of treatment with Zacras	End date of treatment with Zacras - start date of treatment with Zacras + 1
End date of treatment	End date of the final dose described in the column of the end date of treatment in the CRF; or start date of treatment + 360 days if the end date of treatment is not described in the CRF and there is a check for "ongoing at 12 months after the start of treatment with Zacras."
Treatment completer	Patient with a duration of treatment with Zacras of ≥ start date of treatment + 360 days
Treatment non-completer	Patient with a duration of treatment with Zacras of ≤ start date of treatment +

Term	Definition
	359 days
Reason for discontinuation of treatment with Zacras	If the duration of treatment with Zacras is ≤ start date of treatment + 359 days, the reason for discontinuation of treatment described in the column of details on the use of Zacras in the CRF will be employed. If the duration of treatment with Zacras is ≥ start date of treatment + 360 days, the patient will be handled as a treatment completer; therefore, the reason for discontinuation of treatment described in the column of details on the use of Zacras in the CRF will not be employed.
Azilsartan and amlodipine besilate (hereinafter referred to as amlodipine) used before the start of treatment with Zacras	Antihypertensives other than Zacras that are terminated on the start day of treatment with Zacras or the previous day. Antihypertensives other than Zacras will be classified as described below based on the ingredients and their doses listed below. Fixed-dose combinations will also be classified based on individual ingredients and their doses. Azilsartan 20 mg, amlodipine 2.5 mg, amlodipine 5 mg, combined use of azilsartan 20 mg/amlodipine 2.5 mg, combined use of azilsartan 20 mg/amlodipine 5 mg, other
Switching to Zacras (by ingredient/dose)	Switching to Zacras will be classified as described below based on the combination of "azilsartan and amlodipine used before the start of treatment with Zacras" and "initial dose of Zacras." Azilsartan 20 mg→Zacras LD, azilsartan 20 mg→Zacras HD, amlodipine 2.5 mg→Zacras LD, amlodipine 5 mg→Zacras HD, combined use of azilsartan 20 mg/amlodipine 2.5 mg→Zacras LD, combined use of azilsartan 20 mg/amlodipine 5 mg→Zacras HD, other
Switching to Zacras (by ingredient)	Switching to Zacras will be classified as described below based on "switching to Zacras (by ingredient/dose)." "Aazilsartan→Zacras" for "azilsartan 20 mg→Zacras LD" or "azilsartan 20 mg→Zacras HD" "Amlodipine→Zacras" for "amlodipine 2.5 mg→Zacras LD" or "amlodipine 5 mg→Zacras HD" "Combined use of azilsartan/amlodipine→Zacras" for "combined use of azilsartan 20 mg/amlodipine 2.5 mg→Zacras LD" or "combined use of azilsartan 20 mg/amlodipine 5 mg→Zacras HD" "Other" for "other"
Patient who switches from combined use	Patient with "combined use of azilsartan/amlodipine→Zacras" for switching to Zacras (by ingredient)

Term	Definition
Duration of disease	(Start date of treatment with Zacras - time of diagnosis of hypertension + 1) ÷ 365.25. For time of diagnosis of hypertension, 1 will be used as the day, and January 1 will be used if the month is unknown. The duration of disease will be handled as missing if the year, month, and day are unknown.
ADR, etc.	Abbreviation of "adverse drug reaction/infection" AE other than those assessed by the investigator to be not related to Zacras In this document, "adverse drug reaction/infection" is used in titles, and "adverse drug reaction, etc." is used in the text and tables.
SAE	Adverse event assessed by the investigator to be serious Events included in the MedDRA code list in Takeda Medically Significant AE List will be handled as serious even if assessed by the investigator to be non-serious.
Number of patients with an AE or an ADR, etc.	Number of patients who experienced an AE or an ADR, etc.
Number of AE or ADR, etc.	Number of reported AE or ADR, etc.
Time of onset	Time of onset will be calculated as date of onset of AE (or ADR, etc.) - start date of treatment + 1. If the month and day of AE (or ADR, etc.) are unknown, January 1 will be used for calculation. If an AE (or ADR, etc.) occurs in the same year as treatment is started, the month and day of starting treatment will be used for calculation. If the day of AE (or ADR, etc.) is unknown, 1 will be used for calculation. If an AE (or ADR, etc.) occurs in the same year and month as treatment is started, the start date of treatment will be used for calculation. If the year, month, and day of AE (or ADR, etc.) is unknown, the start date of treatment will be used for calculation.
Patient with concurrent diabetes	Patient with a check for diabetes in the column of concurrent illness in the CRF or concurrent illness corresponding to Standardised MedDRA query (hereinafter referred to as SMQ) code 20000041 (hyperglycaemia/new onset diabetes mellitus SMQ [scope: narrow]) described
Patient with concurrent dyslipidemia	Patient with a check for dyslipidemia in the column of concurrent illness in the CRF or concurrent illness corresponding to SMQ code 20000026 (dyslipidaemia SMQ [scope: narrow]) described
Patient with concurrent hyperuricemia	Patient with a check for hyperuricemia in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10020903 (hyperuricaemia) described

Term	Definition
Patient with concurrent cardiac failure	Patient with a check for cardiac failure in the column of concurrent illness in the CRF or concurrent illness corresponding to SMQ code 20000004 (cardiac failure SMQ [scope: narrow]) described in the column of other disease: name of disease
Patient with concurrent coronary artery disease	Patient with a check for myocardial infarction or angina in the column of concurrent illness in the CRF, concurrent illness corresponding to SMQ code 20000043 (ischaemic heart disease SMQ [scope: narrow]) described in the column of other disease: name of disease, or PT corresponding to SMQ code 20000047 (myocardial infarction SMQ [scope: narrow]) described in the column of medical history
Patient with concurrent myocardial infarction (including old myocardial infarction)	Patient with a check for myocardial infarction in the column of concurrent illness in the CRF or PT corresponding to SMQ code 20000047 (myocardial infarction SMQ [scope: narrow]) described in the column of other disease: name of disease or medical history
Patient with concurrent angina	Patient with a check for angina in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10002383 (angina pectoris), 10002388 (angina unstable), 10036759 (Prinzmetal angina), or 10058144 (postinfarction angina) described in the column of other disease: name of disease
Patient with concurrent coronary artery disease (other)	Patient with concurrent coronary artery disease who is not a patient with concurrent myocardial infarction (including old myocardial infarction) or angina
Patient with concurrent atrial fibrillation	Patient with a check for atrial fibrillation in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10003658 (atrial fibrillation) described in the column of other disease: name of disease
Patient with concurrent renal impairment	Patient with a check for chronic kidney disease (CKD), diabetic nephropathy, nephrosclerosis, or other in the column of concurrent illness in the CRF or concurrent illness corresponding to the following (1), (2), or (3) described in the column of other disease: name of disease: (1) SMQ code 20000213 (chronic kidney disease SMQ [scope: narrow]) (2) Takeda MedDRA query (hereinafter referred to as TMQ) (Renal Disease) (3) TMQ (Renal Impairment)
Patient with concurrent chronic kidney disease	Patient with a check for chronic kidney disease (CKD), diabetic nephropathy, nephrosclerosis, or other in the column of concurrent illness in the CRF or

Term	Definition
(CKD)	concurrent illness corresponding to SMQ code 20000213 (chronic kidney disease SMQ [scope: narrow]) described in the column of other disease: name of disease
Patient with concurrent diabetic nephropathy	Patient with a check for diabetic nephropathy in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10061835 (diabetic nephropathy) described in the column of other disease: name of disease
Patient with concurrent nephrosclerosis	Patient with a check for nephrosclerosis in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10029159 (nephrosclerosis) described in the column of other disease: name of disease
Patient with concurrent chronic kidney disease (CKD) (other)	Patient with concurrent chronic kidney disease (CKD) who is not a patient with concurrent diabetic nephropathy or nephrosclerosis
Patient with concurrent renal impairment (other)	Patient with concurrent renal impairment who is not a patient with concurrent chronic kidney disease (CKD), diabetic nephropathy, nephrosclerosis, or chronic kidney disease (CKD) (other)
Patient with concurrent hepatic impairment	Patient with a check for hepatic steatosis or alcoholic hepatopathy in the column of concurrent illness in the CRF or concurrent illness corresponding to the following (1), (2), or (3) described in the column of other disease: name of disease: (1) SMQ code 20000005 (hepatic disorders SMQ [scope: narrow]) (2) MedDRA PT code 10019708 (hepatic steatosis) MedDRA PT code 10001627 (alcoholic liver disease)
Patient with concurrent hepatic steatosis	Patient with a check for hepatic steatosis in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10019708 (hepatic steatosis) described in the column of other disease: name of disease
Patient with concurrent alcoholic hepatopathy	Patient with a check for alcoholic hepatopathy in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10001627 (alcoholic liver disease) described in the column of other disease: name of disease
Patient with concurrent hepatic impairment (other)	Patient with concurrent hepatic impairment who is not a patient with concurrent hepatic steatosis or alcoholic hepatopathy
Patient with concurrent cerebrovascular disorder	Patient with PT corresponding to SMQ code 20000060 (cerebrovascular disorders SMQ [scope: narrow]) described in the column of concurrent

Term	Definition
	illness: other disease: name of disease or medical history in the CRF
Age	If the month and day of starting treatment is smaller than the month and day of birth, age will be calculated as year of starting treatment - year of birth - 1. If the month and day of starting treatment is equal to or greater than the month and day of birth, age will be calculated as year of starting treatment - year of birth. If the month and day of birth is unknown, January 1 will be used for calculation. If the day of birth is unknown, 1 will be used for calculation.
Young, middle-aged, or young-old patient	Patient aged 15 years or older and 74 years or younger
Old-old patient	Patient aged 75 years or older
BMI	BMI will be calculated as body weight (kg) / [0.0001 × height (cm) × height (cm)]. BMI will be displayed to one decimal place by rounding.
Concomitant drug (at the start of treatment with Zacras)	Concomitant drug that is started before the start of treatment with Zacras and is not terminated on the day before the start of treatment with Zacras, or concomitant drug that is started on the start day of treatment with Zacras
Concomitant drug (during the survey period)	Concomitant drug used during a period from the start day of treatment with Zacras to the end day of treatment with Zacras
Concomitant drug (at the end of treatment with Zacras)	Concomitant drug used on the end day of treatment with Zacras
Antihypertensive used within 2 months before the start of treatment with Zacras	Drug described in the column for details on the use of other antihypertensive in the CRF that is started before the start day of treatment with Zacras and used within 2 months (60 days) before the start of treatment with Zacras (excluding drugs that are started on the start day of treatment with Zacras)
Antidiabetic	Drugs with a NHI drug code starting with 396, 2492, or 249941
Antidyslipidemic	Drugs with a NHI drug code starting with 218 or any of the following 7-digit numbers: 2190101, 2190102, 2190103, 2190104
Antihyperuricemic	Drugs with a NHI drug code starting with 394
Antihypertensive	ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics (thiazide and thiazide analogue diuretics), calcium antagonists (hereinafter referred to as Ca antagonists), direct renin inhibitors, aldosterone antagonists/potassium-sparing diuretics, vasodilators, β-blockers, central sympathetic inhibitors, αβ-blockers, α_1-blockers, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose

Term	Definition
	combination: Ca antagonist + statin, and fixed-dose combination: ARB + Ca antagonist + diuretic in a list of antihypertensives in the Guidelines for the Management of Hypertension 2014 (JSH2014)
ACE inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 4-digit number: 2144 Generic name: captopril, enalapril maleate, perindopril erbumine, lisinopril hydrate, alacepril, delapril hydrochloride, benazepril hydrochloride, cilazapril hydrate, imidapril hydrochloride, temocapril hydrochloride, quinapril hydrochloride, trandolapril
ARB	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149039, 2149040, 2149041, 2149042, 2149044, 2149046, 2149048, 2149110, 2149111, 2149112, 2149113, 2149119, 2149116, 2149114, 2149117, 2149118, 2149115, 2149120, 2149122 Generic name: losartan potassium, candesartan cilexetil, valsartan, telmisartan, olmesartan medoxomil, irbesartan, azilsartan, losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, irbesartan/trichlormethiazide, candesartan cilexetil/amlodipine besilate, valsartan/amlodipine besilate, telmisartan/amlodipine besilate, irbesartan/amlodipine besilate, olmesartan medoxomil/azelnidipine, valsartan/cilnidipine, azilsartan/amlodipine besilate, telmisartan/amlodipine besilate/hydrochlorothiazide
Diuretic (thiazide and thiazide analogue diuretic)	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2132003, 2132004, 2132006, 2149103, 2149012, 2135001, 2149007, 2149003, 2149110, 2149111, 2149112, 2149113, 2149119, 2149122 Generic name: trichlormethiazide, hydrochlorothiazide, benzylhydrochlorothiazide, indapamide, mefruside, tripamide, meticrane, losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, irbesartan/trichlormethiazide, telmisartan/amlodipine besilate/hydrochlorothiazide

Term	Definition
HCTZ	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2132004, 2149110, 2149111, 2149112, 2149113, 2149122 Generic name: hydrochlorothiazide, losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, telmisartan/amlodipine besilate/hydrochlorothiazide
Dose of HCTZ	The dose of HCTZ is the maximum dose in patients receiving HCTZ.
Ca antagonist	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2171022, 2171014, 2171019, 2171020, 2149019, 2149022, 2149043, 2149027, 2149034, 2149037, 2149038, 2171021, 2149035, 2149030, 2171006, 2149116, 2149114, 2149117, 2149118, 2149115, 2190101, 2190102, 2190103, 2190104, 2149120, 2149122 Generic name: amlodipine besilate, nifedipine, nisoldipine, nitrendipine, nicardipine hydrochloride, nilvadipine, azelnidipine, manidipine hydrochloride, efonidipine hydrochloride ethanol, cilnidipine, aranidipine, benidipine hydrochloride, felodipine, barnidipine hydrochloride, diltiazem hydrochloride, candesartan cilexetil/amlodipine besilate, valsartan/amlodipine besilate, telmisartan/amlodipine besilate, irbesartan/amlodipine besilate, olmesartan medoxomil/azelnidipine, amlodipine besilate/atorvastatin calcium hydrate, valsartan/cilnidipine, telmisartan/amlodipine besilate/hydrochlorothiazide
Direct renin inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2149047 Generic name: aliskiren fumarate
Aldosterone antagonist/potassium-sparing diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2133001, 2149045, 2133002 Generic name: spironolactone, eplerenone, triamterene
Aldosterone antagonist	Drugs described in the column for details on the use of other

Term	Definition
	antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2133001, 2149045, Generic name: spironolactone, eplerenone
Potassium-sparing diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2133002 Generic name: triamterene
Diuretic	Diuretics (thiazide and thiazide analogue diuretics) or potassium-sparing diuretics described in the column for details on the use of other antihypertensive in the CRF
Vasodilator	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2142004 Generic name: hydralazine hydrochloride
β-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2123011, 2123016, 2149700, 2149031, 2149010, 2123001, 2149029, 2123008, 2149014, 2149021, 2149028, 2123015, 2123005, 2149025, 2123009, 2149011 Generic name: atenolol, bisoprolol fumarate, bisoprolol, betaxolol hydrochloride, metoprolol tartrate, acebutolol hydrochloride, celiprolol hydrochloride, propranolol hydrochloride, nipradilol, tilisolol hydrochloride, nadolol, carteolol hydrochloride, pindolol
Central sympathetic inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149001, 2149017, 2145001 Generic name: clonidine hydrochloride, guanabenz acetate, methyldopa hydrate
αβ-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers:

Term	Definition
	2149032, 2149018, 2123014, 2149009, 2149036 Generic name: carvedilol, amosulalol hydrochloride, arotinolol hydrochloride, labetalol hydrochloride, bevantolol hydrochloride
α_1-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149026, 2149015, 2149023, 2149002, 2149020 Generic name: doxazosin mesilate, bunazosin hydrochloride, terazosin hydrochloride hydrate, prazosin hydrochloride, urapidil
Fixed-dose combination: ARB + diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149110, 2149111, 2149112, 2149113, 2149119, 2149122 Generic name: losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, irbesartan/trichlormethiazide, telmisartan/amlodipine besilate/hydrochlorothiazide
Fixed-dose combination: ARB + Ca antagonist	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149116, 2149114, 2149117, 2149118, 2149115, 2149120, 2149122 Generic name: candesartan cilexetil/amlodipine besilate, valsartan/amlodipine besilate, telmisartan/amlodipine besilate, irbesartan/amlodipine besilate, olmesartan medoxomil/azelnidipine, valsartan/cilnidipine, telmisartan/amlodipine besilate/hydrochlorothiazide
Fixed-dose combination: ARB + Ca antagonist + diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2149122 Generic name: telmisartan/amlodipine besilate/hydrochlorothiazide
Fixed-dose combination: Ca antagonist + statin	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2190101, 2190102, 2190103, 2190104 Generic name: amlodipine besilate/atorvastatin calcium hydrate
Other (antihypertensive)	Vasodilators, β-blockers, central sympathetic inhibitors, αβ-blockers, and

Term	Definition
	α_1-blockers described in the column for details on the use of other antihypertensive in the CRF
Number of concomitant drugs (antihypertensive other than Zacras)	The number of drugs described in the column for details on the use of other antihypertensive in the CRF will be tabulated. The fixed-dose combination will be tabulated as one drug. For instance, "fixed-dose combination: ARB + diuretic" used concomitantly will be tabulated as one drug.
eGFR (mL/min/1.73 m^2)	eGFR will be calculated as 194 × serum creatinine [mg/dL]$^{-1.094}$ × age [years]$^{-0.287}$ (× 0.739 for females). eGFR will be displayed as an integer by rounding.
Summary statistics	Number of patients, mean, standard deviation, minimum, first quartile, median, third quartile, maximum

1.2 Number of Digits to be Displayed

Term	Definition
Percentage (%)	Incidence of AE or ADR, etc.: Displayed to two decimal places by rounding Other: Displayed to one decimal place by rounding
Summary statistics	Mean, median, first quartile, and third quartile: Displayed to one lower digit than raw data by rounding Standard deviation: Displayed to two lower digits than raw data by rounding Minimum and maximum: Displayed to the same number of digits as raw data
P-value	P-value will be displayed to three decimal places by rounding down. P-value rounded down to less than 0.001 will be displayed as $p<0.001$.

1.3 Level of Significance, Confidence Coefficient

Level of significance: 5% (two-sided test)

Confidence coefficient: 95% (two-sided estimate)

1.4 Handling of Test/Measurement Data

Test/measurement data will be handled in accordance with the criteria described below (with 1 month as 30 days). If there are multiple pieces of data at the same specified time point, data on the test day closest to the specified day of assessment will be employed, and the latest data among different pieces of data on different days with the same deviation from the specified day of assessment will be

employed. At the final assessment*, values measured on the day closest to the start date of treatment with Zacras + 374 days will be employed. Values measured 15 days or more after the end day of treatment with Zacras will not be employed.

The number of days from the start day of treatment with Zacras is 1 day for the start day of treatment with Zacras and -1 day for the previous day.

* After 12 months of treatment with Zacras (or at discontinuation of treatment with Zacras)

Time point of test	Permissible range (number of days from the start day of treatment)	Specified day of assessment
At the start of treatment	-90 to 1	Start date of treatment
After 1 month of treatment	2 to 45	Start date of treatment + 30
After 2 months of treatment	46 to 75	Start date of treatment + 60
After 3 months of treatment	76 to 105	Start date of treatment + 90
After 4 months of treatment	106 to 135	Start date of treatment + 120
After 5 months of treatment	136 to 165	Start date of treatment + 150
After 6 months of treatment	166 to 195	Start date of treatment + 180
After 7 months of treatment	196 to 225	Start date of treatment + 210
After 8 months of treatment	226 to 255	Start date of treatment + 240
After 9 months of treatment	256 to 285	Start date of treatment + 270
After 10 months of treatment	286 to 315	Start date of treatment + 300
After 11 months of treatment	316 to 345	Start date of treatment + 330
After 12 months of treatment	346 to 375	Start date of treatment + 360
At the final assessment	2 to 375	Start date of treatment + 374

2.0 Disposition of Patients (Patient Composition Diagram)

(1) Patients included in tabulation/analysis

Enrolled patients

(2) Data tabulated/analyzed

The number of enrolled patients, number of medical institutions involved in patient registration, number of patients from whom the CRF is collected, number of patients from whom the CRF is not collected, number of finalized patients, number of non-finalized patients, number of patients included in safety evaluation, number of patients excluded from safety evaluation, number of patients included in efficacy evaluation, and number of patients excluded from efficacy evaluation will be tabulated.

For the number of medical institutions involved in patient registration, one medical institution with different departments should not be counted more than once.

For patients from whom the CRF is not collected, the number of patients by reason for failure to collect will be tabulated.

For patients excluded from safety evaluation and those excluded from efficacy evaluation, the number of patients by reason for exclusion will be tabulated, and excluded patients will be listed.

Patients meeting any of the criteria listed below will be handled as described below regarding whether to employ them or not.

Criterion	Safety evaluation	Efficacy evaluation
Prescription before the contract period [posterior finding]	×	×
Registration 15 days or more after prescription of Zacras [posterior finding]	×	×
Non-target disease	○	×
Deviation from exclusion criteria	○	×
Failure to confirm the intake of Zacras [after the patient enrollment period]	×	×
Unavailability of follow-up CRF	○	○
It is unknown whether the patient experienced an AE	×	×

○: employed, ×: excluded or not employed

(3) Table/figure number

Figure 2.0-1, Table 2.0-1

3.0 Patient Demographics and Baseline Characteristics

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

For each variable, patients will be categorized as described below, and the number and proportion of patients will be tabulated.

Variable	Category
Sex	Male, female
Age	Summary statistics
	<65 years, ≥65 years
	<65 years, 65 to <75 years, ≥75 years
Duration of disease	<1 year, 1 to <3 years, 3 to <5 years, ≥5 years, unknown
Diagnostic category (at the start of treatment with Zacras)	Outpatient, inpatient
Predisposition to hypersensitivity	No, yes, unknown
Concurrent illness	No, yes
Disposition (multiple tabulation)	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease (myocardial infarction (including old myocardial infarction), angina, or other), atrial fibrillation, renal impairment (chronic kidney disease (CKD) [diabetic nephropathy, nephrosclerosis, or other] or other), hepatic impairment (hepatic steatosis, alcoholic hepatopathy, or other), cerebrovascular disorder
Medical history	No, yes, unknown
Body weight (kg)	Summary statistics
	<40, 40 to <50, 50 to <60, 60 to <70, ≥70, not measured
BMI (kg/m^2)	Summary statistics
	<18.5, 18.5 to <25.0, 25.0 to <30.0, ≥30.0, unknown
eGFR [at the start of treatment] ($mL/min/1.73\ m^2$)	Summary statistics
	<15, 15 to <30, 30 to <45, 45 to <60, 60 to <90, ≥90, unknown
Smoking history	Never smoked, current smoker, past smoker, unknown
Drinking history (drink alcoholic beverage almost every day)	Yes, no, unknown

Presence or absence of breast-feeding (at the start of treatment with Zacras) [only females]	No, yes

(3) Table/figure number

Table 3.0-1

4.0 Treatment Given

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

For each variable, patients will be categorized as described below, and the number and proportion of patients will be tabulated.

Variable	Category
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Disposition	LD→HD, HD→LD, LD→HD→LD, HD→LD→HD * This categorization is an example and subject to change depending on actual data.
Duration of treatment with Zacras	1 to 180 days, 181 to 360 days, ≥361 days
Presence or absence of discontinuation of treatment with Zacras	No, yes
Reason for discontinuation of treatment with Zacras	Successful achievement of treatment goal, AE, patient's failure to visit the hospital such as transfer to another hospital, insufficient efficacy, other
Azilsartan and amlodipine used before the start of treatment with Zacras	Azilsartan 20 mg, amlodipine 2.5 mg, amlodipine 5 mg, combined use of azilsartan 20 mg/amlodipine 2.5 mg, combined use of azilsartan 20 mg/amlodipine 5 mg, other
Switching to Zacras (by ingredient/dose)	Azilsartan 20 mg→Zacras LD, azilsartan 20 mg→Zacras HD, amlodipine 2.5 mg→Zacras LD, amlodipine 5 mg→Zacras HD, combined use of azilsartan 20 mg/amlodipine 2.5 mg→Zacras LD, combined use of azilsartan 20 mg/amlodipine 5 mg→Zacras HD, other
Switching to Zacras (by ingredient)	Azilsartan→Zacras, amlodipine→Zacras, combined use of azilsartan/amlodipine→Zacras, other
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes

Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: ARB + Ca antagonist + diuretic, fixed-dose combination: Ca antagonist + statin, other
Antihypertensive other than Zacras: treatment with HCTZ (at the start of treatment with Zacras)	No, yes
Disposition	6.25 mg, 12.5 mg, other
Treatment with antihypertensive other than Zacras (during the survey period)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: ARB + Ca antagonist + diuretic, fixed-dose combination: Ca antagonist + statin, other
Antihypertensive other than Zacras: treatment with HCTZ (during the survey period)	No, yes
Disposition	6.25 mg, 12.5 mg, other
Treatment with antihypertensive other than Zacras (within 2 months before the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic,

	fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: ARB + Ca antagonist + diuretic, fixed-dose combination: Ca antagonist + statin, other
Number of concomitant drugs (antihypertensive other than Zacras)	
(at the start of treatment with Zacras)	0, 1, 2, 3, 4, 5, ≥6
(at the end of treatment with Zacras)	0, 1, 2, 3, 4, 5, ≥6
Concomitant non-antihypertensive drug (during the survey period)	No, yes
Disposition (multiple tabulation)	Antidiabetic, antidyslipidemic, antihyperuricemic, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If "fixed-dose combination: ARB + diuretic" is used concomitantly, for instance, "ARB" and "diuretic" will also be tabulated.

(3) Table/figure number

Table 4.0-1

5.0 Tabulation/Analysis of Safety

5.1 Occurrence of Adverse Events and Adverse Drug Reactions/Infections

5.1.1 Occurrence of Adverse Events

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an AE	Number of patients who experienced an AE
Number of AE	Number of reported AE. Multiple episodes of the same AE (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of AE	The incidence of AE will be calculated as number of patients with an AE/number of patients included in safety evaluation × 100.
Type of AE	AEs will be classified by SOC and then tabulated by PT. For laboratory tests, AEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an AE and the incidence of AE will be listed by SOC internationally agreed order. For PT, the number of patients with an AE and the incidence of AE will be listed in ascending order of PT code. Multiple episodes of the same AE (PT) in the same patient will be tabulated as 1 patient.

(3) Table/figure number

Table 5.1-1

5.1.2 Occurrence of Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an ADR, etc.	Number of patients who experienced an ADR, etc.
Number of ADR, etc.	Number of reported ADR, etc. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of ADR, etc.	The incidence of ADR, etc. will be calculated as number of patients

	with an ADR, etc./number of patients included in safety evaluation × 100.
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an ADR, etc. and the incidence of ADR, etc. will be listed by SOC internationally agreed order. For PT, the number of patients with ADR, etc. and the incidence of ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as 1 patient.

(3) Table/figure number

Table 5.1-2

5.2 Occurrence of Adverse Events and Adverse Drug Reactions/Infections in Patients Excluded from Safety Evaluation

5.2.1 Occurrence of Adverse Events

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an AE	Number of patients who experienced an AE
Number of AE	Number of reported AE. Multiple episodes of the same AE (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of AE	The incidence of AE will be calculated as number of patients with an AE/number of patients excluded from safety evaluation × 100.
Type of AE	AEs will be classified by SOC and then tabulated by PT. For laboratory tests, AEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an AE and the incidence of AE will be listed by SOC internationally agreed order. For PT, the number of patients with an AE and the incidence of AE will be listed in ascending order of PT code. Multiple episodes of the same AE (PT) in the same patient will be tabulated as 1 patient.

(3) Table/figure number

Table 5.2-1

5.2.2 Occurrence of Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an ADR, etc.	Number of patients who experienced an ADR, etc.
Number of ADR, etc.	Number of reported ADR, etc. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of ADR, etc.	The incidence of ADR, etc. will be calculated as number of patients with an ADR, etc./number of patients excluded from safety evaluation × 100.
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an ADR, etc. and the incidence of ADR, etc. will be listed by SOC internationally agreed order. For PT, the number of patients with ADR, etc. and the incidence of ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as 1 patient.

(3) Table/figure number

Table 5.2-2

5.3 Occurrence of Adverse Events and Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

5.3.1 Occurrence of Adverse Events by Seriousness, Time of Onset, and Outcome

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

AEs will be categorized for each variable as described below, and the type of AE will be tabulated.

Variable	Category
Seriousness	Serious, non-serious
Time of onset	Days 1 to 180, Days 181 to 360, Day 361 or later
Outcome	Recovered, recovering, not recovered, recovered with sequelae, fatal, unknown

The type of AE will be tabulated as described below.

Variable	Data tabulated/analyzed
Number of patients	Number of patients who experienced an AE by SOC/PT
Number of AE	Number of reported AE by SOC/PT
Type of AE	AEs will be classified by SOC and then tabulated by PT. For laboratory tests, AEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. AEs will be listed for SOC by SOC internationally agreed order and for PT in ascending order of PT code. Multiple episodes of the same AE (PT) in the same patient will be tabulated by category as the total number of episodes (for instance, one episode of serious diarrhoea and one episode of non-serious diarrhoea in the same patient will be counted once in the respective categories).

(3) Table/figure number

Table 5.3-1

5.3.2 Occurrence of Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

ADRs, etc. will be categorized for each variable as described below, and the type of ADR will be tabulated.

Variable	Category
Seriousness	Serious, non-serious
Time of onset	Days 1 to 180, Days 181 to 360, Day 361 or later
Outcome	Recovered, recovering, not recovered, recovered with sequelae, fatal, unknown

The type of ADR, etc. will be tabulated as described below.

Variable	Data tabulated/analyzed
Number of patients	Number of patients who experienced an ADR, etc. by SOC/PT
Number of ADR, etc.	Number of reported ADR, etc. by SOC/PT
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. ADRs, etc. will be listed for SOC by SOC internationally agreed order and for PT in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated by category as the total number of episodes (for instance, one episode of serious diarrhoea and one episode of non-serious diarrhoea in the same patient will be counted once in the respective categories).

(3) Table/figure number

Table 5.3-2

5.4 Incidence of Adverse Drug Reaction/Infection by Factors Related to Patient Demographics and Baseline Characteristics and Treatment Given

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

ADRs, etc. will be categorized for each variable as described below, and the incidence of ADR, etc. will be tabulated.

ADRs, etc. will be categorized for each variable as described below, and the type of ADR, etc. will be tabulated. The type of ADR, etc. will be tabulated as described in Section 5.1. For disposition of treatment with antihypertensive other than Zacras (at the start of treatment with Zacras) and disposition of treatment with antihypertensive other than Zacras (during the survey period), "other" will not be tabulated.

Variable	Category
Sex	Male, female
Age	<65 years, ≥65 years
	<65 years, 65 to <75 years, ≥75 years
Predisposition to hypersensitivity	No, yes, unknown
Concurrent illness	No, yes
Disposition	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease, atrial fibrillation, renal impairment, hepatic impairment, cerebrovascular disorder
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Switching to Zacras (by ingredient)	Azilsartan→Zacras, amlodipine→Zacras, combined use of azilsartan/amlodipine→Zacras, other
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic, Ca antagonist, other
Treatment with	No, yes

antihypertensive other than Zacras (during the survey period)	
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic, Ca antagonist, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If "fixed-dose combination: ARB + diuretic" is used concomitantly, for instance, "ARB" and "diuretic" will also be tabulated.

(3) Table/figure number

Tables 5.4.2-1 to -26

5.5 Listing of Occurrence of Serious Adverse Events and Serious Adverse Drug Reactions/Infections

5.5.1 Occurrence of Serious Adverse Events

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a SAE	Number of patients who experienced a SAE
Number of SAE	Number of reported SAE Multiple episodes of the same SAE (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of SAE	The incidence of SAE will be calculated as number of patients with a SAE/number of patients included in safety evaluation × 100.
Type of SAE	SAEs will be classified by SOC and then tabulated by PT. For laboratory tests, SAEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a SAE and the incidence of SAE will be listed by SOC internationally agreed order. For PT, the number of patients with a SAE and the incidence of SAE will be listed in ascending order of PT code. Multiple episodes of the same SAE (PT) in the same patient will be tabulated as 1 patient. The number of patients with a SAE not related to Zacras will be presented in parentheses.

(3) Table/figure number

Table 5.5-1

5.5.2 Occurrence of Serious Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a serious ADR, etc.	Number of patients who experienced a serious ADR, etc.
Number of serious ADR,	Number of reported serious ADR, etc.

etc.	Multiple episodes of the same serious ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of serious ADR, etc.	The incidence of serious ADR, etc. will be calculated as number of patients with a serious ADR, etc./number of patients included in safety evaluation × 100.
Type of serious ADR, etc.	Serious ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, serious ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a serious ADR, etc. and the incidence of serious ADR, etc. will be listed by SOC internationally agreed order. For PT, the number of patients with a serious ADR, etc. and the incidence of serious ADR, etc. will be listed in ascending order of PT code.

(3) Table/figure number

Table 5.5-2

5.6 Listing of Occurrence of Serious Adverse Events and Serious Adverse Drug Reactions/Infections in Patients Excluded from Safety Evaluation

5.6.1 Occurrence of Serious Adverse Events

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a SAE	Number of patients who experienced a SAE
Number of SAE	Number of reported SAE Multiple episodes of the same SAE (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of SAE	The incidence of SAE will be calculated as number of patients with a SAE/number of patients included in safety evaluation × 100.
Type of SAE	SAEs will be classified by SOC and then tabulated by PT. For laboratory tests, SAEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a SAE and the incidence of

	SAE will be listed by SOC internationally agreed order. For PT, the number of patients with a SAE and the incidence of SAE will be listed in ascending order of PT code. Multiple episodes of the same SAE (PT) in the same patient will be tabulated as 1 patient. The number of patients with a SAE not related to Zacras will be presented in parentheses.

(3) Table/figure number

Table 5.6-1

5.6.2 Occurrence of Serious Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a serious ADR, etc.	Number of patients who experienced a serious ADR, etc.
Number of serious ADR, etc.	Number of reported serious ADR, etc. Multiple episodes of the same serious ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of serious ADR, etc.	The incidence of serious ADR, etc. will be calculated as number of patients with a serious ADR, etc./number of patients included in safety evaluation × 100.
Type of serious ADR, etc.	Serious ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, serious ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a serious ADR, etc. and the incidence of serious ADR, etc. will be listed by SOC internationally agreed order. For PT, the number of patients with a serious ADR, etc. and the incidence of serious ADR, etc. will be listed in ascending order of PT code.

(3) Table/figure number

Table 5.6-2

5.7 Changes in Test/Measurement Data over Time

5.7.1 Vital Signs (Pulse Rate)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For pulse rate (bpm), summary statistics will be calculated for measured values at each time point of measurement [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics will be calculated.

(3) Table/figure number

Table 5.7-1

5.7.2 Laboratory Tests

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For white blood cell count, platelet count, AST, ALT, γ-GTP, serum creatinine, BUN, and serum potassium, summary statistics will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics will be calculated.

(3) Table/figure number

Table 5.7-2

6.0 Tabulation/Analysis of Efficacy

6.1 Changes in Blood Pressure over Time

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For systolic and diastolic blood pressure, summary statistics and 95% CI for the mean will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. The mean and standard deviation of test data will be illustrated.

In addition, the proportion of patients with normal blood pressure at each time point of test will be tabulated. The proportion of patients with normal blood pressure will be illustrated. A patient with normal blood pressure is defined as a patient meeting both criteria listed below. A patient with missing data on systolic and/or diastolic blood pressure will be handled as a patient with missing data.

•Systolic blood pressure <140 mmHg

•Diastolic blood pressure <90 mmHg

(3) Table/figure number

Table 6.1.1, Table 6.1.2, Figure 6.1.1, Figure 6.1.2

6.2 Changes in Blood Pressure over Time in Patients Who Switch from the Combined Use of Azilsartan and Amlodipine

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation who switch from combined use

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For systolic and diastolic blood pressure, summary statistics and 95% CI for the mean will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics and 95% CI for the mean will be calculated. The mean and standard deviation of test data and change will be illustrated. The percentage change from the start of treatment with Zacras ((test data at each time point of test - test data at the start of treatment with Zacras) ÷ test data at the start of treatment with Zacras × 100), summary statistics will be calculated. The proportion of patients with normal blood pressure at each time point of test will be tabulated. The proportion of patients with normal blood pressure

will be illustrated.

(3) Table/figure number

Table 6.2.1, Table 6.2.2, Table 6.2.3, Figure 6.2.1-1, Figure 6.2.1-2, Figure 6.2.3

6.3 Changes in Blood Pressure over Time in Patients Except for Those Who Switch from the Combined Use of Azilsartan and Amlodipine

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation except for those who switch from combined use

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For systolic and diastolic blood pressure, summary statistics and 95% CI for the mean will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics and 95% CI for the mean will be calculated, and the paired t-test will be performed. The mean and standard deviation of test data and change will be illustrated. For the percentage change from the start of treatment with Zacras, summary statistics will be calculated.

The proportion of patients with normal blood pressure at each time point of test will be tabulated. The proportion of patients with normal blood pressure will be illustrated.

(3) Table/figure number

Table 6.3.1, Table 6.3.2, Table 6.3.3, Figure 6.3.1-1, Figure 6.3.1-2, Figure 6.3.3

6.4 Factors that May Affect the Efficacy

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For test data on systolic and diastolic blood pressure at the final assessment, summary statistics and 95% CI for the mean will be calculated by the variables listed below.

Variable	Category
Sex	Male, female
Age	<65 years, ≥65 years
	<65 years, 65 to <75 years, ≥75 years
Concurrent illness	No, yes

Disposition (multiple tabulation)	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease, atrial fibrillation, renal impairment, hepatic impairment, cerebrovascular disorder
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic, Ca antagonist, other
Treatment with antihypertensive other than Zacras (during the survey period)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic, Ca antagonist, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If "fixed-dose combination: ARB + diuretic" is used concomitantly, for instance, "ARB" and "diuretic" will also be tabulated.

(3) Table/figure number

Table 6.4.1

Statistical Analysis Plan

Specified Drug-Use Survey (“Long-Term Use Survey”) on Zacras Combination Tablets LD & HD

PPD

Takeda Pharmaceutical Company Limited

PPD

2nd edition prepared on 16 October 2017

Table of Contents

1.0 Definitions of Terms, etc. and Handling of Test/Measurement Data

1.1 Definitions

Term	Definition
Zacras	Zacras Combination Tablets are abbreviated as Zacras in this document.
SOC	System organ class listed in the MedDRA/J
HLGT	High level group term listed in the MedDRA/J
PT	Preferred term listed in the MedDRA/J
LLT	Lowest level term listed in the MedDRA/J
Enrolled patient	Patient allowed to be enrolled
Patient from whom the CRF is collected	Patient from whom the CRF has been obtained
Patient from whom the CRF is not collected	Enrolled patient from whom the CRF has not been collected
Finalized patient	Patient from whom the CRF is collected who has the date of CRF completion entered into the PMS system or who requires no information on the CRF status and has not been excluded from the survey
Non-finalized patient	Patient from whom the CRF is collected who has not been finalized
Patient included in safety evaluation	Finalized patient who is included in safety evaluation
Patient excluded from safety evaluation	Finalized patient who is excluded from safety evaluation
Patient included in efficacy evaluation	Patient included in safety evaluation who is included in efficacy evaluation
Patient excluded from efficacy evaluation	Patient included in safety evaluation who is excluded from safety evaluation
Presence or absence of change in daily dose of Zacras	"Yes" for patients with a change in daily dose between the start of treatment with Zacras and the final assessment
Duration of treatment with Zacras	End date of treatment with Zacras - start date of treatment with Zacras + 1
End date of treatment	End date of the final dose described in the column of the end date of treatment in the CRF; or start date of treatment + 360 days if the end date of treatment is not described in the CRF and there is a check for "ongoing at 12 months after the start of treatment with Zacras."
Treatment completer	Patient with a duration of treatment with Zacras of ≥ start date of treatment + 360 days
Treatment non-completer	Patient with a duration of treatment with Zacras of ≤ start date of treatment +

Term	Definition
	359 days
Reason for discontinuation of treatment with Zacras	If the duration of treatment with Zacras is ≤ start date of treatment + 359 days, the reason for discontinuation of treatment described in the column of details on the use of Zacras in the CRF will be employed. If the duration of treatment with Zacras is ≥ start date of treatment + 360 days, the patient will be handled as a treatment completer; therefore, the reason for discontinuation of treatment described in the column of details on the use of Zacras in the CRF will not be employed.
Azilsartan and amlodipine besilate (hereinafter referred to as amlodipine) used before the start of treatment with Zacras	Antihypertensives other than Zacras that are terminated on the start day of treatment with Zacras or the previous day. Antihypertensives other than Zacras will be classified as described below based on the ingredients and their doses listed below. Fixed-dose combinations will also be classified based on individual ingredients and their doses. Azilsartan 20 mg, amlodipine 2.5 mg, amlodipine 5 mg, combined use of azilsartan 20 mg/amlodipine 2.5 mg, combined use of azilsartan 20 mg/amlodipine 5 mg, other
Switching to Zacras (by ingredient/dose)	Switching to Zacras will be classified as described below based on the combination of "azilsartan and amlodipine used before the start of treatment with Zacras" and "initial dose of Zacras." Azilsartan 20 mg→Zacras LD, azilsartan 20 mg→Zacras HD, amlodipine 2.5 mg→Zacras LD, amlodipine 5 mg→Zacras HD, combined use of azilsartan 20 mg/amlodipine 2.5 mg→Zacras LD, combined use of azilsartan 20 mg/amlodipine 5 mg→Zacras HD, other
Switching to Zacras (by ingredient)	Switching to Zacras will be classified as described below based on "switching to Zacras (by ingredient/dose)." "Aazilsartan→Zacras" for "azilsartan 20 mg→Zacras LD" or "azilsartan 20 mg→Zacras HD" "Amlodipine→Zacras" for "amlodipine 2.5 mg→Zacras LD" or "amlodipine 5 mg→Zacras HD" "Combined use of azilsartan/amlodipine→Zacras" for "combined use of azilsartan 20 mg/amlodipine 2.5 mg→Zacras LD" or "combined use of azilsartan 20 mg/amlodipine 5 mg→Zacras HD" "Other" for "other"
Patient who switches from combined use	Patient with "combined use of azilsartan/amlodipine→Zacras" for switching to Zacras (by ingredient)

Term	Definition
Duration of disease	(Start date of treatment with Zacras - time of diagnosis of hypertension + 1) ÷ 365.25. For time of diagnosis of hypertension, 1 will be used as the day, and January 1 will be used if the month is unknown. The duration of disease will be handled as missing if the year, month, and day are unknown.
ADR, etc.	Abbreviation of "adverse drug reaction/infection" AE other than those assessed by the investigator to be not related to Zacras In this document, "adverse drug reaction/infection" is used in titles, and "adverse drug reaction, etc." is used in the text and tables.
SAE	Adverse event assessed by the investigator to be serious Events included in the MedDRA code list in Takeda Medically Significant AE List will be handled as serious even if assessed by the investigator to be non-serious.
Number of patients with an AE or an ADR, etc.	Number of patients who experienced an AE or an ADR, etc.
Number of AE or ADR, etc.	Number of reported AE or ADR, etc.
Time of onset	Time of onset will be calculated as date of onset of AE (or ADR, etc.) - start date of treatment + 1. If the month and day of AE (or ADR, etc.) are unknown, January 1 will be used for calculation. If an AE (or ADR, etc.) occurs in the same year as treatment is started, the month and day of starting treatment will be used for calculation. If the day of AE (or ADR, etc.) is unknown, 1 will be used for calculation. If an AE (or ADR, etc.) occurs in the same year and month as treatment is started, the start date of treatment will be used for calculation. If the year, month, and day of AE (or ADR, etc.) is unknown, the start date of treatment will be used for calculation.
Patient with concurrent diabetes	Patient with a check for diabetes in the column of concurrent illness in the CRF or concurrent illness corresponding to Standardised MedDRA query (hereinafter referred to as SMQ) code 20000041 (hyperglycaemia/new onset diabetes mellitus SMQ [scope: narrow]) described
Patient with concurrent dyslipidemia	Patient with a check for dyslipidemia in the column of concurrent illness in the CRF or concurrent illness corresponding to SMQ code 20000026 (dyslipidaemia SMQ [scope: narrow]) described
Patient with concurrent hyperuricemia	Patient with a check for hyperuricemia in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10020903 (hyperuricaemia) described

Term	Definition
Patient with concurrent cardiac failure	Patient with a check for cardiac failure in the column of concurrent illness in the CRF or concurrent illness corresponding to SMQ code 20000004 (cardiac failure SMQ [scope: narrow]) described in the column of other disease: name of disease
Patient with concurrent coronary artery disease	Patient with a check for myocardial infarction or angina in the column of concurrent illness in the CRF, concurrent illness corresponding to SMQ code 20000043 (ischaemic heart disease SMQ [scope: narrow]) described in the column of other disease: name of disease, or PT corresponding to SMQ code 20000047 (myocardial infarction SMQ [scope: narrow]) described in the column of medical history
Patient with concurrent myocardial infarction (including old myocardial infarction)	Patient with a check for myocardial infarction in the column of concurrent illness in the CRF or PT corresponding to SMQ code 20000047 (myocardial infarction SMQ [scope: narrow]) described in the column of other disease: name of disease or medical history
Patient with concurrent angina	Patient with a check for angina in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10002383 (angina pectoris), 10002388 (angina unstable), 10036759 (Prinzmetal angina), or 10058144 (postinfarction angina) described in the column of other disease: name of disease
Patient with concurrent coronary artery disease (other)	Patient with concurrent coronary artery disease who is not a patient with concurrent myocardial infarction (including old myocardial infarction) or angina
Patient with concurrent atrial fibrillation	Patient with a check for atrial fibrillation in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10003658 (atrial fibrillation) described in the column of other disease: name of disease
Patient with concurrent renal impairment	Patient with a check for chronic kidney disease (CKD), diabetic nephropathy, nephrosclerosis, or other in the column of concurrent illness in the CRF or concurrent illness corresponding to the following (1), (2), or (3) described in the column of other disease: name of disease: (1) SMQ code 20000213 (chronic kidney disease SMQ [scope: narrow]) (2) Takeda MedDRA query (hereinafter referred to as TMQ) (Renal Disease) (3) TMQ (Renal Impairment)
Patient with concurrent chronic kidney disease	Patient with a check for chronic kidney disease (CKD), diabetic nephropathy, nephrosclerosis, or other in the column of concurrent illness in the CRF or

Term	Definition
(CKD)	concurrent illness corresponding to SMQ code 20000213 (chronic kidney disease SMQ [scope: narrow]) described in the column of other disease: name of disease
Patient with concurrent diabetic nephropathy	Patient with a check for diabetic nephropathy in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10061835 (diabetic nephropathy) described in the column of other disease: name of disease
Patient with concurrent nephrosclerosis	Patient with a check for nephrosclerosis in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10029159 (nephrosclerosis) described in the column of other disease: name of disease
Patient with concurrent chronic kidney disease (CKD) (other)	Patient with concurrent chronic kidney disease (CKD) who is not a patient with concurrent diabetic nephropathy or nephrosclerosis
Patient with concurrent renal impairment (other)	Patient with concurrent renal impairment who is not a patient with concurrent chronic kidney disease (CKD), diabetic nephropathy, nephrosclerosis, or chronic kidney disease (CKD) (other)
Patient with concurrent hepatic impairment	Patient with a check for hepatic steatosis or alcoholic hepatopathy in the column of concurrent illness in the CRF or concurrent illness corresponding to the following (1), (2), or (3) described in the column of other disease: name of disease: (1) SMQ code 20000005 (hepatic disorders SMQ [scope: narrow]) (2) MedDRA PT code 10019708 (hepatic steatosis) MedDRA PT code 10001627 (alcoholic liver disease)
Patient with concurrent hepatic steatosis	Patient with a check for hepatic steatosis in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10019708 (hepatic steatosis) described in the column of other disease: name of disease
Patient with concurrent alcoholic hepatopathy	Patient with a check for alcoholic hepatopathy in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10001627 (alcoholic liver disease) described in the column of other disease: name of disease
Patient with concurrent hepatic impairment (other)	Patient with concurrent hepatic impairment who is not a patient with concurrent hepatic steatosis or alcoholic hepatopathy
Patient with concurrent cerebrovascular disorder	Patient with PT corresponding to SMQ code 20000060 (cerebrovascular disorders SMQ [scope: narrow]) described in the column of concurrent

Term	Definition
	illness: other disease: name of disease or medical history in the CRF
Age	If the month and day of starting treatment is smaller than the month and day of birth, age will be calculated as year of starting treatment - year of birth - 1. If the month and day of starting treatment is equal to or greater than the month and day of birth, age will be calculated as year of starting treatment - year of birth. If the month and day of birth is unknown, January 1 will be used for calculation. If the day of birth is unknown, 1 will be used for calculation.
Young, middle-aged, or young-old patient	Patient aged 15 years or older and 74 years or younger
Old-old patient	Patient aged 75 years or older
BMI	BMI will be calculated as body weight (kg) / [0.0001 × height (cm) × height (cm)]. BMI will be displayed to one decimal place by rounding.
Concomitant drug (at the start of treatment with Zacras)	Concomitant drug that is started before the start of treatment with Zacras and is not terminated on the day before the start of treatment with Zacras, or concomitant drug that is started on the start day of treatment with Zacras
Concomitant drug (during the survey period)	Concomitant drug used during a period from the start day of treatment with Zacras to the end day of treatment with Zacras
Concomitant drug (at the end of treatment with Zacras)	Concomitant drug used on the end day of treatment with Zacras
Antihypertensive used within 2 months before the start of treatment with Zacras	Drug described in the column for details on the use of other antihypertensive in the CRF that is started before the start day of treatment with Zacras and used within 2 months (60 days) before the start of treatment with Zacras (excluding drugs that are started on the start day of treatment with Zacras)
Antidiabetic	Drugs with a NHI drug code starting with 396, 2492, or 249941
Antidyslipidemic	Drugs with a NHI drug code starting with 218 or any of the following 7-digit numbers: 2190101, 2190102, 2190103, 2190104
Antihyperuricemic	Drugs with a NHI drug code starting with 394
Antihypertensive	ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics (thiazide and thiazide analogue diuretics), calcium antagonists (hereinafter referred to as Ca antagonists), direct renin inhibitors, aldosterone antagonists/potassium-sparing diuretics, vasodilators, β-blockers, central sympathetic inhibitors, αβ-blockers, α_1-blockers, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose

Term	Definition
	combination: Ca antagonist + statin, and fixed-dose combination: ARB + Ca antagonist + diuretic in a list of antihypertensives in the Guidelines for the Management of Hypertension 2014 (JSH2014)
ACE inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 4-digit number: 2144 Generic name: captopril, enalapril maleate, perindopril erbumine, lisinopril hydrate, alacepril, delapril hydrochloride, benazepril hydrochloride, cilazapril hydrate, imidapril hydrochloride, temocapril hydrochloride, quinapril hydrochloride, trandolapril
ARB	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149039, 2149040, 2149041, 2149042, 2149044, 2149046, 2149048, 2149110, 2149111, 2149112, 2149113, 2149119, 2149116, 2149114, 2149117, 2149118, 2149115, 2149120, 2149122 Generic name: losartan potassium, candesartan cilexetil, valsartan, telmisartan, olmesartan medoxomil, irbesartan, azilsartan, losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, irbesartan/trichlormethiazide, candesartan cilexetil/amlodipine besilate, valsartan/amlodipine besilate, telmisartan/amlodipine besilate, irbesartan/amlodipine besilate, olmesartan medoxomil/azelnidipine, valsartan/cilnidipine, azilsartan/amlodipine besilate, telmisartan/amlodipine besilate/hydrochlorothiazide
Diuretic (thiazide and thiazide analogue diuretic)	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2132003, 2132004, 2132006, 2149103, 2149012, 2135001, 2149007, 2149003, 2149110, 2149111, 2149112, 2149113, 2149119, 2149122 Generic name: trichlormethiazide, hydrochlorothiazide, benzylhydrochlorothiazide, indapamide, mefruside, tripamide, meticrane, losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, irbesartan/trichlormethiazide, telmisartan/amlodipine besilate/hydrochlorothiazide

Term	Definition
HCTZ	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2132004, 2149110, 2149111, 2149112, 2149113, 2149122 Generic name: hydrochlorothiazide, losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, telmisartan/amlodipine besilate/hydrochlorothiazide
Dose of HCTZ	The dose of HCTZ is the maximum dose in patients receiving HCTZ.
Ca antagonist	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2171022, 2171014, 2171019, 2171020, 2149019, 2149022, 2149043, 2149027, 2149034, 2149037, 2149038, 2171021, 2149035, 2149030, 2171006, 2149116, 2149114, 2149117, 2149118, 2149115, 2190101, 2190102, 2190103, 2190104, 2149120, 2149122 Generic name: amlodipine besilate, nifedipine, nisoldipine, nitrendipine, nicardipine hydrochloride, nilvadipine, azelnidipine, manidipine hydrochloride, efonidipine hydrochloride ethanol, cilnidipine, aranidipine, benidipine hydrochloride, felodipine, barnidipine hydrochloride, diltiazem hydrochloride, candesartan cilexetil/amlodipine besilate, valsartan/amlodipine besilate, telmisartan/amlodipine besilate, irbesartan/amlodipine besilate, olmesartan medoxomil/azelnidipine, amlodipine besilate/atorvastatin calcium hydrate, valsartan/cilnidipine, telmisartan/amlodipine besilate/hydrochlorothiazide
Direct renin inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2149047 Generic name: aliskiren fumarate
Aldosterone antagonist/potassium-sparing diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2133001, 2149045, 2133002 Generic name: spironolactone, eplerenone, triamterene
Aldosterone antagonist	Drugs described in the column for details on the use of other

Term	Definition
	antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2133001, 2149045, Generic name: spironolactone, eplerenone
Potassium-sparing diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2133002 Generic name: triamterene
Diuretic	Diuretics (thiazide and thiazide analogue diuretics) or potassium-sparing diuretics described in the column for details on the use of other antihypertensive in the CRF
Vasodilator	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2142004 Generic name: hydralazine hydrochloride
β-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2123011, 2123016, 2149700, 2149031, 2149010, 2123001, 2149029, 2123008, 2149014, 2149021, 2149028, 2123015, 2123005, 2149025, 2123009, 2149011 Generic name: atenolol, bisoprolol fumarate, bisoprolol, betaxolol hydrochloride, metoprolol tartrate, acebutolol hydrochloride, celiprolol hydrochloride, propranolol hydrochloride, nipradilol, tilisolol hydrochloride, nadolol, carteolol hydrochloride, pindolol
Central sympathetic inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149001, 2149017, 2145001 Generic name: clonidine hydrochloride, guanabenz acetate, methyldopa hydrate
αβ-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers:

Term	Definition
	2149032, 2149018, 2123014, 2149009, 2149036 Generic name: carvedilol, amosulalol hydrochloride, arotinolol hydrochloride, labetalol hydrochloride, bevantolol hydrochloride
α_1-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149026, 2149015, 2149023, 2149002, 2149020 Generic name: doxazosin mesilate, bunazosin hydrochloride, terazosin hydrochloride hydrate, prazosin hydrochloride, urapidil
Fixed-dose combination: ARB + diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149110, 2149111, 2149112, 2149113, 2149119, 2149122 Generic name: losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, irbesartan/trichlormethiazide, telmisartan/amlodipine besilate/hydrochlorothiazide
Fixed-dose combination: ARB + Ca antagonist	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149116, 2149114, 2149117, 2149118, 2149115, 2149120, 2149122 Generic name: candesartan cilexetil/amlodipine besilate, valsartan/amlodipine besilate, telmisartan/amlodipine besilate, irbesartan/amlodipine besilate, olmesartan medoxomil/azelnidipine, valsartan/cilnidipine, telmisartan/amlodipine besilate/hydrochlorothiazide
Fixed-dose combination: ARB + Ca antagonist + diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2149122 Generic name: telmisartan/amlodipine besilate/hydrochlorothiazide
Fixed-dose combination: Ca antagonist + statin	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2190101, 2190102, 2190103, 2190104 Generic name: amlodipine besilate/atorvastatin calcium hydrate
Other (antihypertensive)	Vasodilators, β-blockers, central sympathetic inhibitors, αβ-blockers, and

Term	Definition
	α_1-blockers described in the column for details on the use of other antihypertensive in the CRF
Number of concomitant drugs (antihypertensive other than Zacras)	The number of drugs described in the column for details on the use of other antihypertensive in the CRF will be tabulated. The fixed-dose combination will be tabulated as one drug. For instance, "fixed-dose combination: ARB + diuretic" used concomitantly will be tabulated as one drug.
eGFR (mL/min/1.73 m^2)	eGFR will be calculated as 194 × serum creatinine [mg/dL]$^{-1.094}$ × age [years]$^{-0.287}$ (× 0.739 for females). eGFR will be displayed as an integer by rounding.
Summary statistics	Number of patients, mean, standard deviation, minimum, first quartile, median, third quartile, maximum

1.2 Number of Digits to be Displayed

Term	Definition
Percentage (%)	Incidence of AE or ADR, etc.: Displayed to two decimal places by rounding Other: Displayed to one decimal place by rounding
Summary statistics	Mean, median, first quartile, and third quartile: Displayed to one lower digit than raw data by rounding Standard deviation: Displayed to two lower digits than raw data by rounding Minimum and maximum: Displayed to the same number of digits as raw data
P-value	P-value will be displayed to three decimal places by rounding down. P-value rounded down to less than 0.001 will be displayed as $p<0.001$.

1.3 Level of Significance, Confidence Coefficient

Level of significance: 5% (two-sided test)

Confidence coefficient: 95% (two-sided estimate)

1.4 Handling of Test/Measurement Data

Test/measurement data will be handled in accordance with the criteria described below (with 1 month as 30 days). If there are multiple pieces of data at the same specified time point, data on the test day closest to the specified day of assessment will be employed, and the latest data among different pieces of data on different days with the same deviation from the specified day of assessment will be

employed. At the final assessment*, values measured on the day closest to the start date of treatment with Zacras + 375 days will be employed. Values measured 16 days or more after the end day of treatment with Zacras will not be employed.

The number of days from the start day of treatment with Zacras is 1 day for the start day of treatment with Zacras and -1 day for the previous day.

* After 12 months of treatment with Zacras (or at discontinuation of treatment with Zacras)

Time point of test	Permissible range (number of days from the start day of treatment)	Specified day of assessment
At the start of treatment	-90 to -1	Start date of treatment
After 1 month of treatment	2 to 45	Start date of treatment + 30
After 2 months of treatment	46 to 75	Start date of treatment + 60
After 3 months of treatment	76 to 105	Start date of treatment + 90
After 4 months of treatment	106 to 135	Start date of treatment + 120
After 5 months of treatment	136 to 165	Start date of treatment + 150
After 6 months of treatment	166 to 195	Start date of treatment + 180
After 7 months of treatment	196 to 225	Start date of treatment + 210
After 8 months of treatment	226 to 255	Start date of treatment + 240
After 9 months of treatment	256 to 285	Start date of treatment + 270
After 10 months of treatment	286 to 315	Start date of treatment + 300
After 11 months of treatment	316 to 345	Start date of treatment + 330
After 12 months of treatment	346 to 375	Start date of treatment + 360
At the final assessment	1 to 375	Start date of treatment + 375

2.0 Disposition of Patients (Patient Composition Diagram)

(1) Patients included in tabulation/analysis

Enrolled patients

(2) Data tabulated/analyzed

The number of enrolled patients, number of medical institutions involved in patient registration, number of patients from whom the CRF is collected, number of patients from whom the CRF is not collected, number of finalized patients, number of non-finalized patients, number of patients included in safety evaluation, number of patients excluded from safety evaluation, number of patients included in efficacy evaluation, and number of patients excluded from efficacy evaluation will be tabulated.

For the number of medical institutions involved in patient registration, one medical institution with different departments should not be counted more than once.

For patients from whom the CRF is not collected, the number of patients by reason for failure to collect will be tabulated.

For patients excluded from safety evaluation and those excluded from efficacy evaluation, the number of patients by reason for exclusion will be tabulated, and excluded patients will be listed.

Patients meeting any of the criteria listed below will be handled as described below regarding whether to employ them or not.

Criterion	Safety evaluation	Efficacy evaluation
Prescription before the contract period [posterior finding]	×	×
Registration 15 days or more after prescription of Zacras [posterior finding]	×	×
Non-target disease	○	×
Deviation from exclusion criteria	○	×
Failure to confirm the intake of Zacras [after the patient enrollment period]	×	×
Unavailability of follow-up CRF	○	○
It is unknown whether the patient experienced an AE	×	×

○: employed, ×: excluded or not employed

(3) Table/figure number

Figure 2.0-1, Table 2.0-1

3.0 Patient Demographics and Baseline Characteristics

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

For each variable, patients will be categorized as described below, and the number and proportion of patients will be tabulated.

Variable	Category
Sex	Male, female
Age	Summary statistics
	<65 years, ≥65 years
	<65 years, 65 to <75 years, ≥75 years
Duration of disease	<1 year, 1 to <3 years, 3 to <5 years, ≥5 years, unknown
Diagnostic category (at the start of treatment with Zacras)	Outpatient, inpatient
Predisposition to hypersensitivity	No, yes, unknown
Concurrent illness	No, yes
Disposition (multiple tabulation)	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease (myocardial infarction (including old myocardial infarction), angina, or other), atrial fibrillation, renal impairment (chronic kidney disease (CKD) [diabetic nephropathy, nephrosclerosis, or other] or other), hepatic impairment (hepatic steatosis, alcoholic hepatopathy, or other), cerebrovascular disorder
Medical history	No, yes, unknown
Body weight (kg)	Summary statistics
	<40, 40 to <50, 50 to <60, 60 to <70, ≥70, not measured
BMI (kg/m^2)	Summary statistics
	<18.5, 18.5 to <25.0, 25.0 to <30.0, ≥30.0, unknown
eGFR [at the start of treatment] ($mL/min/1.73\ m^2$)	Summary statistics
	<15, 15 to <30, 30 to <45, 45 to <60, 60 to <90, ≥90, unknown
Smoking history	Never smoked, current smoker, past smoker, unknown
Drinking history (drink alcoholic beverage almost every day)	Yes, no, unknown

Presence or absence of breast-feeding (at the start of treatment with Zacras) [only females]	No, yes

(3) Table/figure number

Table 3.0-1

4.0 Treatment Given

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

For each variable, patients will be categorized as described below, and the number and proportion of patients will be tabulated.

Variable	Category
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Disposition	LD→HD, HD→LD, LD→HD→LD, HD→LD→HD * This categorization is an example and subject to change depending on actual data.
Duration of treatment with Zacras	1 to 180 days, 181 to 360 days, ≥361 days
Presence or absence of discontinuation of treatment with Zacras	No, yes
Reason for discontinuation of treatment with Zacras	Successful achievement of treatment goal, AE, patient's failure to visit the hospital such as transfer to another hospital, insufficient efficacy, other
Azilsartan and amlodipine used before the start of treatment with Zacras	Azilsartan 20 mg, amlodipine 2.5 mg, amlodipine 5 mg, combined use of azilsartan 20 mg/amlodipine 2.5 mg, combined use of azilsartan 20 mg/amlodipine 5 mg, other
Switching to Zacras (by ingredient/dose)	Azilsartan 20 mg→Zacras LD, azilsartan 20 mg→Zacras HD, amlodipine 2.5 mg→Zacras LD, amlodipine 5 mg→Zacras HD, combined use of azilsartan 20 mg/amlodipine 2.5 mg→Zacras LD, combined use of azilsartan 20 mg/amlodipine 5 mg→Zacras HD, other
Switching to Zacras (by ingredient)	Azilsartan→Zacras, amlodipine→Zacras, combined use of azilsartan/amlodipine→Zacras, other
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes

Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: ARB + Ca antagonist + diuretic, fixed-dose combination: Ca antagonist + statin, other
Antihypertensive other than Zacras: treatment with HCTZ (at the start of treatment with Zacras)	No, yes
Disposition	6.25 mg, 12.5 mg, other
Treatment with antihypertensive other than Zacras (during the survey period)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: ARB + Ca antagonist + diuretic, fixed-dose combination: Ca antagonist + statin, other
Antihypertensive other than Zacras: treatment with HCTZ (during the survey period)	No, yes
Disposition	6.25 mg, 12.5 mg, other
Treatment with antihypertensive other than Zacras (within 2 months before the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic,

	fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: ARB + Ca antagonist + diuretic, fixed-dose combination: Ca antagonist + statin, other
Number of concomitant drugs (antihypertensive other than Zacras)	
(at the start of treatment with Zacras)	0, 1, 2, 3, 4, 5, ≥6
(at the end of treatment with Zacras)	0, 1, 2, 3, 4, 5, ≥6
Concomitant non-antihypertensive drug (during the survey period)	No, yes
Disposition (multiple tabulation)	Antidiabetic, antidyslipidemic, antihyperuricemic, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If "fixed-dose combination: ARB + diuretic" is used concomitantly, for instance, "ARB" and "diuretic" will also be tabulated.

(3) Table/figure number

Table 4.0-1

5.0 Tabulation/Analysis of Safety

5.1 Occurrence of Adverse Events and Adverse Drug Reactions/Infections

5.1.1 Occurrence of Adverse Events

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an AE	Number of patients who experienced an AE
Number of AE	Number of reported AE. Multiple episodes of the same AE (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of AE	The incidence of AE will be calculated as number of patients with an AE/number of patients included in safety evaluation × 100.
Type of AE	AEs will be classified by SOC and then tabulated by PT. For laboratory tests, AEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an AE and the incidence of AE will be listed by SOC internationally agreed order. For PT, the number of patients with an AE and the incidence of AE will be listed in ascending order of PT code. Multiple episodes of the same AE (PT) in the same patient will be tabulated as 1 patient.

(3) Table/figure number

Table 5.1-1

5.1.2 Occurrence of Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an ADR, etc.	Number of patients who experienced an ADR, etc.
Number of ADR, etc.	Number of reported ADR, etc. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of ADR, etc.	The incidence of ADR, etc. will be calculated as number of patients

	with an ADR, etc./number of patients included in safety evaluation × 100.
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an ADR, etc. and the incidence of ADR, etc. will be listed by SOC internationally agreed order. For PT, the number of patients with ADR, etc. and the incidence of ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as 1 patient.

(3) Table/figure number

Table 5.1-2

5.2 Occurrence of Adverse Events and Adverse Drug Reactions/Infections in Patients Excluded from Safety Evaluation

5.2.1 Occurrence of Adverse Events

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an AE	Number of patients who experienced an AE
Number of AE	Number of reported AE. Multiple episodes of the same AE (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of AE	The incidence of AE will be calculated as number of patients with an AE/number of patients excluded from safety evaluation × 100.
Type of AE	AEs will be classified by SOC and then tabulated by PT. For laboratory tests, AEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an AE and the incidence of AE will be listed by SOC internationally agreed order. For PT, the number of patients with an AE and the incidence of AE will be listed in ascending order of PT code. Multiple episodes of the same AE (PT) in the same patient will be tabulated as 1 patient.

(3) Table/figure number

Table 5.2-1

5.2.2 Occurrence of Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an ADR, etc.	Number of patients who experienced an ADR, etc.
Number of ADR, etc.	Number of reported ADR, etc. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of ADR, etc.	The incidence of ADR, etc. will be calculated as number of patients with an ADR, etc./number of patients excluded from safety evaluation × 100.
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an ADR, etc. and the incidence of ADR, etc. will be listed by SOC internationally agreed order. For PT, the number of patients with ADR, etc. and the incidence of ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as 1 patient.

(3) Table/figure number

Table 5.2-2

5.3 Occurrence of Adverse Events and Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

5.3.1 Occurrence of Adverse Events by Seriousness, Time of Onset, and Outcome

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

AEs will be categorized for each variable as described below, and the type of AE will be tabulated.

Variable	Category
Seriousness	Serious, non-serious
Time of onset	Days 1 to 180, Days 181 to 360, Day 361 or later
Outcome	Recovered, recovering, not recovered, recovered with sequelae, fatal, unknown

The type of AE will be tabulated as described below.

Variable	Data tabulated/analyzed
Number of patients	Number of patients who experienced an AE by SOC/PT
Number of AE	Number of reported AE by SOC/PT
Type of AE	AEs will be classified by SOC and then tabulated by PT. For laboratory tests, AEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. AEs will be listed for SOC by SOC internationally agreed order and for PT in ascending order of PT code. Multiple episodes of the same AE (PT) in the same patient will be tabulated by category as the total number of episodes (for instance, one episode of serious diarrhoea and one episode of non-serious diarrhoea in the same patient will be counted once in the respective categories).

(3) Table/figure number

Table 5.3-1

5.3.2 Occurrence of Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

ADRs, etc. will be categorized for each variable as described below, and the type of ADR will be tabulated.

Variable	Category
Seriousness	Serious, non-serious
Time of onset	Days 1 to 180, Days 181 to 360, Day 361 or later
Outcome	Recovered, recovering, not recovered, recovered with sequelae, fatal, unknown

The type of ADR, etc. will be tabulated as described below.

Variable	Data tabulated/analyzed
Number of patients	Number of patients who experienced an ADR, etc. by SOC/PT
Number of ADR, etc.	Number of reported ADR, etc. by SOC/PT
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. ADRs, etc. will be listed for SOC by SOC internationally agreed order and for PT in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated by category as the total number of episodes (for instance, one episode of serious diarrhoea and one episode of non-serious diarrhoea in the same patient will be counted once in the respective categories).

(3) Table/figure number

Table 5.3-2

5.4 Incidence of Adverse Drug Reaction/Infection by Factors Related to Patient Demographics and Baseline Characteristics and Treatment Given

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

ADRs, etc. will be categorized for each variable as described below, and the incidence of ADR, etc. will be tabulated.

ADRs, etc. will be categorized for each variable as described below, and the type of ADR, etc. will be tabulated. The type of ADR, etc. will be tabulated as described in Section 5.1. For disposition of treatment with antihypertensive other than Zacras (at the start of treatment with Zacras) and disposition of treatment with antihypertensive other than Zacras (during the survey period), "other" will not be tabulated.

Variable	Category
Sex	Male, female
Age	<65 years, ≥65 years
	<65 years, 65 to <75 years, ≥75 years
Predisposition to hypersensitivity	No, yes, unknown
Concurrent illness	No, yes
Disposition	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease, atrial fibrillation, renal impairment, hepatic impairment, cerebrovascular disorder
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Switching to Zacras (by ingredient)	Azilsartan→Zacras, amlodipine→Zacras, combined use of azilsartan/amlodipine→Zacras, other
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic, Ca antagonist, other
Treatment with	No, yes

antihypertensive other than Zacras (during the survey period)	
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic, Ca antagonist, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If "fixed-dose combination: ARB + diuretic" is used concomitantly, for instance, "ARB" and "diuretic" will also be tabulated.

(3) Table/figure number

Tables 5.4.2-1 to -26

5.5 Listing of Occurrence of Serious Adverse Events and Serious Adverse Drug Reactions/Infections

5.5.1 Occurrence of Serious Adverse Events

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a SAE	Number of patients who experienced a SAE
Number of SAE	Number of reported SAE Multiple episodes of the same SAE (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of SAE	The incidence of SAE will be calculated as number of patients with a SAE/number of patients included in safety evaluation × 100.
Type of SAE	SAEs will be classified by SOC and then tabulated by PT. For laboratory tests, SAEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a SAE and the incidence of SAE will be listed by SOC internationally agreed order. For PT, the number of patients with a SAE and the incidence of SAE will be listed in ascending order of PT code. Multiple episodes of the same SAE (PT) in the same patient will be tabulated as 1 patient. The number of patients with a SAE not related to Zacras will be presented in parentheses.

(3) Table/figure number

Table 5.5-1

5.5.2 Occurrence of Serious Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a serious ADR, etc.	Number of patients who experienced a serious ADR, etc.
Number of serious ADR,	Number of reported serious ADR, etc.

etc.	Multiple episodes of the same serious ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of serious ADR, etc.	The incidence of serious ADR, etc. will be calculated as number of patients with a serious ADR, etc./number of patients included in safety evaluation × 100.
Type of serious ADR, etc.	Serious ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, serious ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a serious ADR, etc. and the incidence of serious ADR, etc. will be listed by SOC internationally agreed order. For PT, the number of patients with a serious ADR, etc. and the incidence of serious ADR, etc. will be listed in ascending order of PT code.

(3) Table/figure number

Table 5.5-2

5.6 Listing of Occurrence of Serious Adverse Events and Serious Adverse Drug Reactions/Infections in Patients Excluded from Safety Evaluation

5.6.1 Occurrence of Serious Adverse Events

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a SAE	Number of patients who experienced a SAE
Number of SAE	Number of reported SAE Multiple episodes of the same SAE (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of SAE	The incidence of SAE will be calculated as number of patients with a SAE/number of patients included in safety evaluation × 100.
Type of SAE	SAEs will be classified by SOC and then tabulated by PT. For laboratory tests, SAEs will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a SAE and the incidence of

	SAE will be listed by SOC internationally agreed order. For PT, the number of patients with a SAE and the incidence of SAE will be listed in ascending order of PT code. Multiple episodes of the same SAE (PT) in the same patient will be tabulated as 1 patient. The number of patients with a SAE not related to Zacras will be presented in parentheses.

(3) Table/figure number

Table 5.6-1

5.6.2 Occurrence of Serious Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a serious ADR, etc.	Number of patients who experienced a serious ADR, etc.
Number of serious ADR, etc.	Number of reported serious ADR, etc. Multiple episodes of the same serious ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of serious ADR, etc.	The incidence of serious ADR, etc. will be calculated as number of patients with a serious ADR, etc./number of patients included in safety evaluation × 100.
Type of serious ADR, etc.	Serious ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, serious ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a serious ADR, etc. and the incidence of serious ADR, etc. will be listed by SOC internationally agreed order. For PT, the number of patients with a serious ADR, etc. and the incidence of serious ADR, etc. will be listed in ascending order of PT code.

(3) Table/figure number

Table 5.6-2

5.7 Changes in Test/Measurement Data over Time

5.7.1 Vital Signs (Pulse Rate)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For pulse rate (bpm), summary statistics will be calculated for measured values at each time point of measurement [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics will be calculated.

(3) Table/figure number

Table 5.7-1

5.7.2 Laboratory Tests

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For white blood cell count, platelet count, AST, ALT, γ-GTP, serum creatinine, BUN, and serum potassium, summary statistics will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics will be calculated.

(3) Table/figure number

Table 5.7-2

6.0 Tabulation/Analysis of Efficacy

6.1 Changes in Blood Pressure over Time

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For systolic and diastolic blood pressure, summary statistics and 95% CI for the mean will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. The mean and standard deviation of test data will be illustrated.

In addition, the proportion of patients with normal blood pressure at each time point of test will be tabulated. The proportion of patients with normal blood pressure will be illustrated. A patient with normal blood pressure is defined as a patient meeting both criteria listed below. A patient with missing data on systolic and/or diastolic blood pressure will be handled as a patient with missing data.

•Systolic blood pressure <140 mmHg

•Diastolic blood pressure <90 mmHg

(3) Table/figure number

Table 6.1.1, Table 6.1.2, Figure 6.1.1, Figure 6.1.2

6.2 Changes in Blood Pressure over Time in Patients Who Switch from the Combined Use of Azilsartan and Amlodipine

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation who switch from combined use

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For systolic and diastolic blood pressure, summary statistics and 95% CI for the mean will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics and 95% CI for the mean will be calculated. The mean and standard deviation of test data and change will be illustrated. The percentage change from the start of treatment with Zacras ((test data at each time point of test - test data at the start of treatment with Zacras) ÷ test data at the start of treatment with Zacras × 100), summary statistics will be calculated. The proportion of patients with normal blood pressure at each time point of test will be tabulated. The proportion of patients with normal blood pressure

will be illustrated.

(3) Table/figure number

Table 6.2.1, Table 6.2.2, Table 6.2.3, Figure 6.2.1-1, Figure 6.2.1-2, Figure 6.2.3

6.3 Changes in Blood Pressure over Time in Patients Except for Those Who Switch from the Combined Use of Azilsartan and Amlodipine

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation except for those who switch from combined use

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For systolic and diastolic blood pressure, summary statistics and 95% CI for the mean will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics and 95% CI for the mean will be calculated, and the paired t-test will be performed. The mean and standard deviation of test data and change will be illustrated. For the percentage change from the start of treatment with Zacras, summary statistics will be calculated.

The proportion of patients with normal blood pressure at each time point of test will be tabulated. The proportion of patients with normal blood pressure will be illustrated.

(3) Table/figure number

Table 6.3.1, Table 6.3.2, Table 6.3.3, Figure 6.3.1-1, Figure 6.3.1-2, Figure 6.3.3

6.4 Factors that May Affect the Efficacy

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

Analyses described below will be performed for patients who have relevant data both before and after treatment with Zacras.

For test data on systolic and diastolic blood pressure at the final assessment, summary statistics and 95% CI for the mean will be calculated by the variables listed below.

Variable	Category
Sex	Male, female
Age	<65 years, ≥65 years
	<65 years, 65 to <75 years, ≥75 years
Concurrent illness	No, yes

Disposition (multiple tabulation)	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease, atrial fibrillation, renal impairment, hepatic impairment, cerebrovascular disorder
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic, Ca antagonist, other
Treatment with antihypertensive other than Zacras (during the survey period)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic, Ca antagonist, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If "fixed-dose combination: ARB + diuretic" is used concomitantly, for instance, "ARB" and "diuretic" will also be tabulated.

(3) Table/figure number

Table 6.4.1

Statistical Analysis Plan

Specified Drug-Use Survey (“Long-Term Use Survey”) on Zacras Combination Tablets LD & HD

PPD

Takeda Pharmaceutical Company Limited

PPD

Contract Organization for Statistical Analysis

Responsible Person

PPD

1st edition prepared on 9 December 2014

Table of Contents

1.0 Definitions of Terms, etc. and Handling of Test/Measurement Data

1.1 Definitions

Term	Definition
Zacras	Zacras Combination Tablets are abbreviated as Zacras in this document.
SOC	System organ class listed in the MedDRA/J
HLGT	High level group term listed in the MedDRA/J
PT	Preferred term listed in the MedDRA/J
LLT	Lowest level term listed in the MedDRA/J
Enrolled patient	Patient allowed to be enrolled
Patient from whom the CRF is collected	Patient from whom the CRF has been obtained
Patient from whom the CRF is not collected	Enrolled patient from whom the CRF has not been collected
Finalized patient	Patient from whom the CRF is collected who has the date of CRF completion entered into the PMS system or who requires no information on the CRF status and has not been excluded from the survey
Non-finalized patient	Patient from whom the CRF is collected who has not been finalized
Patient included in safety evaluation	Finalized patient who is included in safety evaluation
Patient excluded from safety evaluation	Finalized patient who is excluded from safety evaluation
Patient included in efficacy evaluation	Patient included in safety evaluation who is included in efficacy evaluation
Patient excluded from efficacy evaluation	Patient included in safety evaluation who meets neither (1) nor (2) (1) Office blood pressure (systolic): Test data are available both before and after[1)] treatment with Zacras. (2) Office blood pressure (diastolic): Test data are available both before and after[1)] treatment with Zacras. [1)] Values measured after the end of treatment with Zacras will not be employed. Values measured during the off-treatment period will be employed.
Presence or absence of change in daily dose of Zacras	"Yes" for patients with a change in daily dose at the final assessment versus at the start of treatment with Zacras
Duration of treatment with Zacras	End date of treatment with Zacras - start date of treatment with Zacras + 1
End date of treatment	End date of the final dose described in the column of the end date of treatment in the CRF; or start date of treatment + 360 days if the end date of

Term	Definition
	treatment is not described in the CRF and there is a check for "ongoing at 12 months after the start of treatment with Zacras."
Off-treatment period	The off-treatment period will be allowed until the end date of treatment before suspension of treatment + 90 days. If the off-treatment period continues beyond the end date of treatment + 90 days, the end date of treatment is defined as the end date of treatment before suspension of treatment.
Treatment completer	Patient with a duration of treatment with Zacras of ≥ start date of treatment + 360 days
Treatment non-completer	Patient with a duration of treatment with Zacras of ≤ start date of treatment + 359 days
Reason for discontinuation of treatment with Zacras	If the duration of treatment with Zacras is ≤ start date of treatment + 359 days, the reason for discontinuation of treatment described in the column of details on the use of Zacras in the CRF will be employed. If the duration of treatment with Zacras is ≥ start date of treatment + 360 days, the patient will be handled as a treatment completer; therefore, the reason for discontinuation of treatment described in the column of details on the use of Zacras in the CRF will not be employed.
Duration of disease	(Start date of treatment with Zacras - time of diagnosis of hypertension + 1) ÷ 365.25. For time of diagnosis of hypertension, 1 will be used as the day, and January 1 will be used if the month is unknown.
AE, etc.	Abbreviation of "adverse event/infection" In this document, "adverse event/infection" is used in titles, and "adverse event, etc." is used in the text and tables.
ADR, etc.	Abbreviation of "adverse drug reaction/infection" AE, etc. other than those assessed by the investigator to be not related to Zacras In this document, "adverse drug reaction/infection" is used in titles, and "adverse drug reaction, etc." is used in the text and tables.
SAE, etc.	Abbreviation of "serious adverse event/infection" Adverse event assessed by the investigator to be serious Events included in the MedDRA code list in Takeda Medically Significant AE List will be handled as serious even if assessed by the investigator to be non-serious. In this document, "serious adverse event/infection" is used in titles, and "serious adverse event, etc." is used in the text and tables.

Term	Definition
Number of patients with an AE, etc. or an ADR, etc.	Number of patients who experienced an AE, etc. or an ADR, etc.
Number of AE, etc. or ADR, etc.	Number of reported AE, etc. or ADR, etc.
Incidence	[When safety is tabulated in patients included in safety evaluation] The incidence will be calculated as number of patients with an AE, etc. or an ADR, etc./number of patients included in safety evaluation × 100. [When safety is tabulated in patients excluded from safety evaluation] The incidence will be calculated as number of patients with an AE, etc. or an ADR, etc./number of patients excluded from safety evaluation × 100. For PT, multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as 1 patient/1 event to calculate the incidence as follows: [When safety is tabulated in patients included in safety evaluation] The incidence will be calculated as number of AE, etc. or ADR, etc./number of patients included in safety evaluation × 100. [When safety is tabulated in patients excluded from safety evaluation] The incidence will be calculated as number of AE, etc. or ADR, etc./number of patients excluded from safety evaluation × 100.
Time of onset	Time of onset will be calculated as date of onset of AE, etc. (or ADR, etc.) - start date of treatment + 1. If the month and day of AE, etc. (or ADR, etc.) is unknown, January 1 will be used for calculation. If an AE, etc. (or ADR, etc.) occurs in the same year as treatment is started, the month and day of starting treatment will be used for calculation. If the day of AE, etc. (or ADR, etc.) is unknown, 1 will be used for calculation. If an AE, etc. (or ADR, etc.) occurs in the same year and month as treatment is started, the start date of treatment will be used for calculation.
Patient with concurrent diabetes	Patient with a check for diabetes in the column of concurrent illness in the CRF or concurrent illness corresponding to SMQ code 20000041 (hyperglycaemia/new onset diabetes mellitus SMQ [scope: narrow]) described
Patient with concurrent dyslipidemia	Patient with a check for dyslipidemia in the column of concurrent illness in the CRF or concurrent illness corresponding to SMQ code 20000026 (dyslipidaemia SMQ [scope: narrow]) described
Patient with concurrent hyperuricemia	Patient with a check for hyperuricemia in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10020903

Term	Definition
	(hyperuricaemia) described
Patient with concurrent coronary artery disease	Patient with a check for myocardial infarction or angina in the column of concurrent illness in the CRF, concurrent illness corresponding to SMQ code 20000043 (ischaemic heart disease SMQ [scope: narrow]) described in the column of other disease: name of disease, or PT corresponding to SMQ code 20000047 (myocardial infarction SMQ [scope: narrow]) described in the column of medical history
Patient with concurrent cardiac failure	Patient with a check for cardiac failure in the column of concurrent illness in the CRF or concurrent illness corresponding to SMQ code 20000004 (cardiac failure SMQ [scope: narrow]) described in the column of other disease: name of disease
Patient with concurrent myocardial infarction (including old myocardial infarction)	Patient with a check for myocardial infarction in the column of concurrent illness in the CRF or PT corresponding to SMQ code 20000047 (myocardial infarction SMQ [scope: narrow]) described in the column of other disease: name of disease or medical history
Patient with concurrent angina	Patient with a check for angina in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10002383 (angina pectoris), 10002388 (angina unstable), 10036759 (Prinzmetal angina), or 10058144 (postinfarction angina) described in the column of other disease: name of disease
Patient with concurrent coronary artery disease (other)	Patient with concurrent coronary artery disease who is not a patient with concurrent myocardial infarction (including old myocardial infarction) or angina
Patient with concurrent atrial fibrillation	Patient with a check for atrial fibrillation in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10003658 (atrial fibrillation) described in the column of other disease: name of disease
Patient with concurrent renal impairment	Patient with a check for chronic kidney disease (CKD), diabetic nephropathy, nephrosclerosis, or other in the column of concurrent illness in the CRF or concurrent illness corresponding to the following (1), (2), or (3) described in the column of other disease: name of disease: (1) SMQ code 20000213 (chronic kidney disease SMQ [scope: narrow]) (2) Takeda MedDRA query (hereinafter referred to as TMQ) (Renal Disease) (3) TMQ (Renal Impairment)
Patient with concurrent	Patient with a check for chronic kidney disease (CKD), diabetic nephropathy,

Term	Definition
chronic kidney disease (CKD)	nephrosclerosis, or other in the column of concurrent illness in the CRF or concurrent illness corresponding to SMQ code 20000213 (chronic kidney disease SMQ [scope: narrow]) described in the column of other disease: name of disease
Patient with concurrent diabetic nephropathy	Patient with a check for diabetic nephropathy in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10061835 (diabetic nephropathy) described in the column of other disease: name of disease
Patient with concurrent nephrosclerosis	Patient with a check for nephrosclerosis in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10029159 (nephrosclerosis) described in the column of other disease: name of disease
Patient with concurrent chronic kidney disease (CKD) (other)	Patient with concurrent chronic kidney disease (CKD) who is not a patient with concurrent diabetic nephropathy or nephrosclerosis
Patient with concurrent renal impairment (other)	Patient with concurrent renal impairment who is not a patient with concurrent chronic kidney disease (CKD), diabetic nephropathy, nephrosclerosis, or chronic kidney disease (CKD) (other)
Patient with concurrent hepatic impairment	Patient with a check for hepatic steatosis or alcoholic hepatopathy in the column of concurrent illness in the CRF or concurrent illness corresponding to the following (1), (2), or (3) described in the column of other disease: name of disease: (1) Standardised MedDRA query (hereinafter referred to as SMQ) code 20000005 (hepatic disorders SMQ [scope: narrow]) (2) MedDRA PT code 10019708 (hepatic steatosis) (3) MedDRA PT code 10001627 (alcoholic liver disease)
Patient with concurrent hepatic steatosis	Patient with a check for hepatic steatosis in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10019708 (hepatic steatosis) described in the column of other disease: name of disease
Patient with concurrent alcoholic hepatopathy	Patient with a check for alcoholic hepatopathy in the column of concurrent illness in the CRF or concurrent illness corresponding to MedDRA PT code 10001627 (alcoholic liver disease) described in the column of other disease: name of disease
Patient with concurrent hepatic impairment (other)	Patient with concurrent hepatic impairment who is not a patient with concurrent hepatic steatosis or alcoholic hepatopathy
Patient with concurrent	Patient with PT corresponding to SMQ code 20000060 (cerebrovascular

Term	Definition
cerebrovascular disorder	disorders SMQ [scope: narrow]) described in the column of concurrent illness: other disease: name of disease or medical history in the CRF
Age	If the month and day of starting treatment is smaller than the month and day of birth, age will be calculated as year of starting treatment - year of birth - 1. If the month and day of starting treatment is equal to or greater than the month and day of birth, age will be calculated as year of starting treatment - year of birth. If the month and day of birth is unknown, January 1 will be used for calculation. If the day of birth is unknown, 1 will be used for calculation.
Young, middle-aged, or young-old patient	Patient aged 15 years or older and 74 years or younger
Old-old patient	Patient aged 75 years or older
BMI	BMI will be calculated as body weight (kg) / [0.0001 × height (cm) × height (cm)]. BMI will be displayed to one decimal place by rounding.
Concomitant drug	Drug used during treatment with Zacras
Concomitant drug (at the start of treatment with Zacras)	Concomitant drug that is started before the start of treatment with Zacras and is not terminated at the start of treatment with Zacras, or concomitant drug that is started on the start day of treatment with Zacras
Concomitant drug (during the survey period)	Concomitant drug used during a period from the start day of treatment with Zacras to the end day of treatment with Zacras, including drugs used during the off-treatment period
Concomitant drug (at the end of treatment with Zacras)	Concomitant drug used on the end day of treatment with Zacras
Antihypertensive used within 2 months before the start of treatment with Zacras	Drug described in the column for details on the use of other antihypertensive in the CRF that is started before the start day of treatment with Zacras and used within 2 months (60 days) before the start of treatment with Zacras (excluding drugs that are started on the start day of treatment with Zacras)
Antidiabetic	Drugs with a NHI drug code starting with 396, 2492, or 249941
Antidyslipidemic	Drugs with a NHI drug code starting with 218 or any of the following 7-digit numbers: 2190101, 2190102, 2190103, 2190104
Antihyperuricemic	Drugs with a NHI drug code starting with 394
Antihypertensive	ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics (thiazide and thiazide analogue diuretics), calcium antagonists (Ca antagonists), direct renin inhibitors, aldosterone antagonists/potassium-sparing diuretics, vasodilators, β-blockers, central sympathetic inhibitors, αβ-blockers,

Term	Definition
	α_1-blockers, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + calcium antagonist (Ca antagonist), and fixed-dose combination: calcium antagonist + statin in a list of antihypertensives in the Guidelines for the Management of Hypertension 2014 (JSH2014)
ACE inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 4-digit number: 2144 Generic name: captopril, enalapril maleate, perindopril erbumine, lisinopril hydrate, alacepril, delapril hydrochloride, benazepril hydrochloride, cilazapril hydrate, imidapril hydrochloride, temocapril hydrochloride, quinapril hydrochloride, trandolapril
ARB	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149039, 2149040, 2149041, 2149042, 2149044, 2149046, 2149048, 2149110, 2149111, 2149112, 2149113, 2149119, 2149116, 2149114, 2149117, 2149118, 2149115, 2149120, 2149121 Generic name: losartan potassium, candesartan cilexetil, valsartan, telmisartan, olmesartan medoxomil, irbesartan, azilsartan
Diuretic (thiazide and thiazide analogue diuretic)	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2132003, 2132004, 2132006, 2149103, 2149012, 2135001, 2149007, 2149003, 2149110, 2149111, 2149112, 2149113, 2149119 Generic name: trichlormethiazide, hydrochlorothiazide, benzylhydrochlorothiazide, indapamide, mefruside, tripamide, meticrane, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide
HCTZ	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2132004, 2149110, 2149111, 2149112, 2149113 Generic name: hydrochlorothiazide, losartan potassium/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide,
Dose of HCTZ	The dose of HCTZ is the maximum dose in patients receiving HCTZ.
Ca antagonist	Drugs described in the column for details on the use of other antihypertensive

Term	Definition
	in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2171022, 2171014, 2171019, 2171020, 2149019, 2149022, 2149043, 2149027, 2149034, 2149037, 2149038, 2171021, 2149035, 2149030, 2171006, 2149116, 2149114, 2149117, 2149118, 2149115, 2190101, 2190102, 2190103, 2190104, 2149120, 2149121 Generic name: amlodipine besilate, nifedipine, nisoldipine, nitrendipine, nicardipine hydrochloride, nilvadipine, azelnidipine, manidipine hydrochloride, efonidipine hydrochloride ethanol, cilnidipine, aranidipine, benidipine hydrochloride, felodipine, barnidipine hydrochloride, diltiazem hydrochloride
Direct renin inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2149047 Generic name: aliskiren fumarate
Aldosterone antagonist/potassium-sparing diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2133001, 2149045, 2133002 Generic name: spironolactone, eplerenone, triamterene
Aldosterone antagonist	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2133001, 2149045, Generic name: spironolactone, eplerenone
Potassium-sparing diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit number: 2133002 Generic name: triamterene
Diuretic	Diuretics (thiazide and thiazide analogue diuretics) or potassium-sparing diuretics described in the column for details on the use of other antihypertensive in the CRF
Vasodilator	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with the following 7-digit

Term	Definition
	number: 2142004 Generic name: hydralazine hydrochloride
β-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2123011, 2123016, 2149700, 2149031, 2149010, 2123001, 2149029, 2123008, 2149014, 2149021, 2149028, 2123015, 2123005, 2149025, 2123009, 2149011 Generic name: atenolol, bisoprolol fumarate, bisoprolol, betaxolol hydrochloride, metoprolol tartrate, acebutolol hydrochloride, celiprolol hydrochloride, propranolol hydrochloride, nipradilol, tilisolol hydrochloride, nadolol, carteolol hydrochloride, pindolol
Central sympathetic inhibitor	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149001, 2149017, 2145001 Generic name: clonidine hydrochloride, guanabenz acetate, methyldopa hydrate
αβ-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149032, 2149018, 2123014, 2149009, 2149036 Generic name: carvedilol, amosulalol hydrochloride, arotinolol hydrochloride, labetalol hydrochloride, bevantolol hydrochloride
α_1-blocker	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149026, 2149015, 2149023, 2149002, 2149020 Generic name: doxazosin mesilate, bunazosin hydrochloride, terazosin hydrochloride hydrate, prazosin hydrochloride, urapidil
Fixed-dose combination: ARB + diuretic	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149110, 2149111, 2149112, 2149113, 2149119 Generic name: losartan potassium/hydrochlorothiazide, candesartan

Term	Definition
	cilexetil/hydrochlorothiazide, valsartan/hydrochlorothiazide, telmisartan/hydrochlorothiazide, irbesartan/trichlormethiazide
Fixed-dose combination: ARB + Ca antagonist	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2149116, 2149114, 2149117, 2149118, 2149115, 2149120 Generic name: candesartan cilexetil/amlodipine besilate, valsartan/amlodipine besilate, telmisartan/amlodipine besilate, irbesartan/amlodipine besilate, olmesartan medoxomil/azelnidipine, valsartan/cilnidipine
Fixed-dose combination: Ca antagonist + statin	Drugs described in the column for details on the use of other antihypertensive in the CRF that have a NHI drug code starting with any of the following 7-digit numbers: 2190101, 2190102, 2190103, 2190104 Generic name: amlodipine besilate/atorvastatin calcium hydrate
Other (antihypertensive)	Vasodilators, β-blockers, central sympathetic inhibitors, αβ-blockers, and α_1-blockers described in the column for details on the use of other antihypertensive in the CRF
Number of concomitant drugs (antihypertensive other than Zacras)	The number of drugs described in the column for details on the use of other antihypertensive in the CRF will be tabulated. The fixed-dose combination will be tabulated as one drug. For instance, "fixed-dose combination: ARB + diuretic" used concomitantly will be tabulated as one drug.
eGFR (mL/min/1.73 m^2)	eGFR will be calculated as 194 × serum creatinine [mg/dL]$^{-1.094}$ × age [years]$^{-0.287}$ (× 0.739 for females). eGFR will be displayed as an integer by rounding.
Summary statistics	Mean, standard deviation, minimum, first quartile, median, third quartile, maximum

1.2 Number of Digits to be Displayed

Term	Definition
Percentage (%)	Incidence of AE, etc. or ADR, etc.: Displayed to two decimal places by rounding Other: Displayed to one decimal place by rounding
Summary statistics (mean/standard deviation)	Mean: Displayed to one lower digit than raw data by rounding Standard deviation:

Term	Definition
	Displayed to two lower digits than raw data by rounding
P-value	P-value will be displayed to three decimal places by rounding down. P-value rounded down to less than 0.001 will be displayed as p<0.001.

1.3 Level of Significance

Two-sided 5%

1.4 Handling of Test/Measurement Data

Test/measurement data will be handled in accordance with the criteria described below (with 1 month as 30 days). If there are multiple pieces of data at the same specified time point, data on the test day closest to the specified day of assessment will be employed, and the latest data among different pieces of data on different days with the same deviation from the specified day of assessment will be employed. At the final assessment*, values measured on the day closest to the start date of treatment with Zacras + 375 days will be employed (including values measured during the off-treatment period). Values measured after the end day of treatment with Zacras will not be employed.

The number of days from the start day of treatment with Zacras is 1 day for the start day of treatment with Zacras and -1 day for the previous day.

* After 12 months of treatment with Zacras (or at discontinuation of treatment with Zacras)

Time point of test	Permissible range (number of days from the start day of treatment)	Specified day of assessment
At the start of treatment	-90 to -1	Start date of treatment
After 1 month of treatment	1 to 45	Start date of treatment + 30
After 2 months of treatment	46 to 75	Start date of treatment + 60
After 3 months of treatment	76 to 105	Start date of treatment + 90
After 4 months of treatment	106 to 135	Start date of treatment + 120
After 5 months of treatment	136 to 165	Start date of treatment + 150
After 6 months of treatment	166 to 195	Start date of treatment + 180
After 7 months of treatment	196 to 225	Start date of treatment + 210
After 8 months of treatment	226 to 255	Start date of treatment + 240
After 9 months of treatment	256 to 285	Start date of treatment + 270
After 10 months of treatment	286 to 315	Start date of treatment + 300
After 11 months of treatment	316 to 345	Start date of treatment + 330
After 12 months of treatment	346 to 375	Start date of treatment + 360

At the final assessment	1 to 375	Start date of treatment + 375

2.0 Disposition of Patients (Patient Composition Diagram)

(1) Patients included in tabulation/analysis

Patients enrolled in the specified drug-use survey

(2) Data tabulated/analyzed

The number of enrolled patients, number of medical institutions involved in patient registration, number of patients from whom the CRF is collected, number of patients from whom the CRF is not collected, number of finalized patients, number of non-finalized patients, number of patients included in safety evaluation, number of patients excluded from safety evaluation, number of patients included in efficacy evaluation, and number of patients excluded from efficacy evaluation will be tabulated.

For the number of medical institutions involved in patient registration, one medical institution with different departments should not be counted more than once.

For patients from whom the CRF is not collected, the number of patients by reason for failure to collect and the total number will be tabulated.

For patients excluded from safety evaluation and those excluded from efficacy evaluation, the number of patients by reason for exclusion and the total number will be tabulated.

Patients meeting any of the criteria listed below will be handled as described below regarding whether to employ them or not.

Criterion	Enrollment	Safety evaluation	Efficacy evaluation
Duplicate registration (the same patient) [posterior finding]	×	-	-
Wrong registration (not prescribed) [posterior finding]	×	-	-
Treatment before the contract period [posterior finding]	○	×	×
Registration after 15 days of treatment with Zacras [posterior finding]	○	×	×
No data on blood pressure before or after treatment with Zacras	○	○	×
Deviation from inclusion criteria	○	○	×
Deviation from exclusion criteria	○	○	×
Failure to confirm the intake of Zacras [during the patient enrollment period]	×	-	-
Failure to confirm the intake of Zacras [after the patient enrollment period]	○	×	×

Unavailability of follow-up CRF	○	○	○

○: employed, ×: excluded or not employed

(3) Table/figure number

Figure 2.0-1, Table 2.0-1

3.0 Patient Demographics and Baseline Characteristics

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

For each variable, patients will be categorized as described below, and the number and proportion of patients will be tabulated.

Variable	Category
Sex	Male, female
Age	Summary statistics
	<65 years, ≥65 years
	<65 years, 65 to 74 years, ≥75 years
Duration of disease	<1 year, 1 to <3 years, 3 to <5 years, ≥5 years, unknown
Diagnostic category (at the start of treatment with Zacras)	Outpatient, inpatient
Predisposition to hypersensitivity	No, yes, unknown
Concurrent illness	No, yes
Disposition (multiple tabulation)	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease (myocardial infarction (including old myocardial infarction), angina, or other), atrial fibrillation, renal impairment (chronic kidney disease (CKD) [diabetic nephropathy, nephrosclerosis, or other] or other), hepatic impairment (hepatic steatosis, alcoholic hepatopathy, or other), cerebrovascular disorder
Medical history	No, yes, unknown
Body weight (kg)	Summary statistics
	<40, 40 to <50, 50 to <60, 60 to <70, ≥70, not measured
BMI (kg/m^2)	Summary statistics
	<18.5, 18.5 to <25.0, 25.0 to <30.0, ≥30.0, unknown
eGFR [at the start of treatment] ($mL/min/1.73\ m^2$)	Summary statistics
	<15, 15 to <30, 30 to <45, 45 to <60, 60 to <90, ≥90, unknown
Smoking history	Never smoked, current smoker, past smoker, unknown
Drinking history (drink alcoholic beverage almost every day)	Yes, no, unknown

Presence or absence of breast-feeding (at the start of treatment with Zacras) [only females]	No, yes

(3) Table/figure number

Table 3.0-1

4.0 Treatment Given

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

For each variable, patients will be categorized as described below, and the number and proportion of patients will be tabulated.

Variable	Category
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Disposition	LD → HD, HD → LD
Duration of treatment with Zacras	1 to 180 days, 181 to 360 days, ≥361 days
Presence or absence of discontinuation of treatment with Zacras	No, yes
Reason for discontinuation of treatment with Zacras	Successful achievement of treatment goal, AE, patient's failure to visit the hospital such as transfer to another hospital, insufficient efficacy, other
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Antihypertensive other than Zacras: treatment with HCTZ (at the start of treatment with Zacras)	No, yes
Disposition	6.25 mg, 12.5 mg, other
Treatment with	No, yes

antihypertensive other than Zacras (during the survey period)	
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Antihypertensive other than Zacras: treatment with HCTZ (during the survey period)	No, yes
Disposition	6.25 mg, 12.5 mg, other
Treatment with antihypertensive other than Zacras (within 2 months before the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Number of concomitant drugs (antihypertensive other than Zacras)	
(at the start of treatment with Zacras)	0, 1, 2, 3, 4, 5, ≥6
(at the end of treatment with Zacras)	0, 1, 2, 3, 4, 5, ≥6
Concomitant non-antihypertensive drug (during the survey period)	No, yes

Disposition (multiple tabulation)	Antidiabetic, antidyslipidemic, antihyperuricemic, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If “fixed-dose combination: ARB + diuretic” is used concomitantly, for instance, “ARB” and “diuretic” will also be tabulated.

(3) Table/figure number

Table 4.0-1

5.0 Tabulation/Analysis of Safety

5.1 Occurrence of Adverse Events/Infections and Adverse Drug Reactions/Infections

5.1.1 Occurrence of Adverse Events/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an AE, etc.	Number of patients who experienced an AE, etc.
Number of AE, etc.	Number of reported AE, etc. Multiple episodes of the same AE, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of AE, etc.	The incidence of AE, etc. will be calculated as number of patients with an AE, etc./number of patients included in safety evaluation × 100.
Type of AE, etc.	AEs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, AEs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an AE, etc. and the incidence of AE, etc. will be listed by SOC internationally agreed order. For PT, the number and incidence of AE, etc. will be listed in ascending order of PT code. Multiple episodes of the same AE, etc. (PT) in the same patient will be tabulated as 1 patient/1 event.

(3) Table/figure number

Table 5.1-1

5.1.2 Occurrence of Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an ADR, etc.	Number of patients who experienced an ADR, etc.
Number of ADR, etc.	Number of reported ADR, etc. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as the total number of

	episodes.
Incidence of ADR, etc.	The incidence of ADR, etc. will be calculated as number of patients with an ADR, etc./number of patients included in safety evaluation × 100.
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an ADR, etc. and the incidence of ADR, etc. will be listed by SOC internationally agreed order. For PT, the number and incidence of ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as 1 patient/1 event.

(3) Table/figure number

Table 5.1-2

5.2 Occurrence of Adverse Events/Infections and Adverse Drug Reactions/Infections in Patients Excluded from Safety Evaluation

5.2.1 Occurrence of Adverse Events/Infections

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an AE, etc.	Number of patients who experienced an AE, etc.
Number of AE, etc.	Number of reported AE, etc. Multiple episodes of the same AE, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of AE, etc.	The incidence of AE, etc. will be calculated as number of patients with an AE, etc./number of patients excluded from safety evaluation × 100.
Type of AE, etc.	AEs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, AEs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an AE, etc. and the incidence of AE, etc. will be listed by SOC internationally agreed order.

	For PT, the number and incidence of AE, etc. will be listed in ascending order of PT code. Multiple episodes of the same AE, etc. (PT) in the same patient will be tabulated as 1 patient/1 event.

(3) Table/figure number

Table 5.2-1

5.2.2 Occurrence of Adverse Drug Reactions/Infections

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with an ADR, etc.	Number of patients who experienced an ADR, etc.
Number of ADR, etc.	Number of reported ADR, etc. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of ADR, etc.	The incidence of ADR, etc. will be calculated as number of patients with an ADR, etc./number of patients excluded from safety evaluation × 100.
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with an ADR, etc. and the incidence of ADR, etc. will be listed by SOC internationally agreed order. For PT, the number and incidence of ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated as 1 patient/1 event.

(3) Table/figure number

Table 5.2-2

5.3 Occurrence of Adverse Events/Infections and Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

5.3.1 Occurrence of Adverse Events/Infections by Seriousness, Time of Onset, and Outcome

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

AEs, etc. will be categorized for each variable as described below, and the type of AE, etc. will be tabulated.

Variable	Category
Seriousness	Serious, non-serious
Time of onset	Days 1 to 180, Days 181 to 360, Day 361 or later
Outcome	Recovered, recovering, not recovered, recovered with sequelae, fatal, unknown

The type of AE, etc. will be tabulated as described below.

Variable	Data tabulated/analyzed
Number of patients	Number of patients who experienced an AE, etc. by SOC/PT
Number of AE, etc.	Number of reported AE, etc. by SOC/PT
Type of AE, etc.	AEs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, AEs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. AEs, etc. will be listed for SOC by SOC internationally agreed order and for PT in ascending order of PT code. Multiple episodes of the same AE, etc. (PT) in the same patient will be tabulated by category as the total number of episodes (for instance, one episode of serious diarrhoea and one episode of non-serious diarrhoea in the same patient will be counted once in the respective categories).

(3) Table/figure number

Table 5.3-1

5.3.2 Occurrence of Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

ADRs, etc. will be categorized for each variable as described below, and the type of ADR, etc. will be tabulated.

Variable	Category
Seriousness	Serious, non-serious
Time of onset	Days 1 to 180, Days 181 to 360, Day 361 or later
Outcome	Recovered, recovering, not recovered, recovered with sequelae, fatal, unknown

The type of ADR, etc. will be tabulated as described below.

Variable	Data tabulated/analyzed
Number of patients	Number of patients who experienced an ADR, etc. by SOC/PT
Number of ADR, etc.	Number of reported ADR, etc. by SOC/PT
Type of ADR, etc.	ADRs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, ADRs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. ADRs, etc. will be listed for SOC by SOC internationally agreed order and for PT in ascending order of PT code. Multiple episodes of the same ADR, etc. (PT) in the same patient will be tabulated by category as the total number of episodes (for instance, one episode of serious diarrhoea and one episode of non-serious diarrhoea in the same patient will be counted once in the respective categories).

(3) Table/figure number

Table 5.3-2

5.4 Incidence of Adverse Event/Infection and Adverse Drug Reaction/Infection by Factors Related to Patient Demographics and Baseline Characteristics and Treatment Given

5.4.1 Incidence of Adverse Event/Infection by Factors Related to Patient Demographics and Baseline Characteristics and Treatment Given

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

AEs, etc. will be categorized for each variable as described below, and the incidence of AE, etc. (point estimate and 95% CI) will be tabulated.

In addition, Fisher's exact probability test will be performed for variables with unranked categories, and the Mann-Whitney U test will be performed for variables with ranked categories.

Variable	Category
Sex	Male, female
Age	<65 years, ≥65 years
	<65 years, 65 to 74 years, ≥75 years
Predisposition to hypersensitivity	No, yes, unknown
Concurrent illness	No, yes

Disposition (multiple tabulation)	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease (myocardial infarction (including old myocardial infarction), angina, or other), atrial fibrillation, renal impairment (chronic kidney disease (CKD) [diabetic nephropathy, nephrosclerosis, or other] or other), hepatic impairment (hepatic steatosis, alcoholic hepatopathy, or other), cerebrovascular disorder
Medical history	No, yes, unknown
Body weight (kg)	<40, 40 to <50, 50 to <60, 60 to <70, ≥70, not measured
BMI (kg/m^2)	<18.5, 18.5 to <25.0, 25.0 to <30.0, ≥30.0, unknown
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Disposition	LD → HD, HD → LD
Duration of treatment with Zacras	1 to 180 days, 181 to 360 days, ≥361 days The denominator is the number of patients treated with Zacras for 1 day or more to calculate the incidence of AE, etc. for "1 to x days" and the number of patients treated with Zacras for x + 1 days or more to calculate the incidence of AE, etc. for "x + 1 to y days."
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Treatment with antihypertensive other than Zacras (during the survey period)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination:

	calcium antagonist + statin, other
Treatment with antihypertensive other than Zacras (within 2 months before the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Concomitant non-antihypertensive drug (during the survey period)	No, yes
Disposition (multiple tabulation)	Antidiabetic, antidyslipidemic, antihyperuricemic, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If "fixed-dose combination: ARB + diuretic" is used concomitantly, for instance, "ARB" and "diuretic" will also be tabulated.

(3) Table/figure number

Table 5.4-1

5.4.2 Incidence of Adverse Drug Reaction/Infection by Factors Related to Patient Demographics and Baseline Characteristics and Treatment Given

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

ADRs, etc. will be categorized for each variable as described below, and the incidence of ADR, etc. (point estimate and 95% CI) will be tabulated.

In addition, Fisher's exact probability test will be performed for variables with unranked categories, and the Mann-Whitney U test will be performed for variables with ranked categories.

Variable	Category

Sex	Male, female
Age	<65 years, ≥65 years
	<65 years, 65 to 74 years, ≥75 years
Predisposition to hypersensitivity	No, yes, unknown
Concurrent illness	No, yes
Disposition	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease (myocardial infarction (including old myocardial infarction), angina, or other), atrial fibrillation, renal impairment (chronic kidney disease (CKD) [diabetic nephropathy, nephrosclerosis, or other] or other), hepatic impairment (hepatic steatosis, alcoholic hepatopathy, or other), cerebrovascular disorder
Medical history	No, yes, unknown
Body weight (kg)	<40, 40 to <50, 50 to <60, 60 to <70, ≥70, not measured
BMI (kg/m^2)	<18.5, 18.5 to <25.0, 25.0 to <30.0, ≥30.0, unknown
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Disposition	LD → HD, HD → LD
Duration of treatment with Zacras	1 to 180 days, 181 to 360 days, ≥361 days The denominator is the number of patients treated with Zacras for 1 day or more to calculate the incidence of AE, etc. for "1 to x days" and the number of patients treated with Zacras for x + 1 days or more to calculate the incidence of AE, etc. for "x + 1 to y days."
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Treatment with antihypertensive other	No, yes

than Zacras (during the survey period)	
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Treatment with antihypertensive other than Zacras (within 2 months before the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Concomitant non-antihypertensive drug (during the survey period)	No, yes
Disposition (multiple tabulation)	Antidiabetic, antidyslipidemic, antihyperuricemic, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If "fixed-dose combination: ARB + diuretic" is used concomitantly, for instance, "ARB" and "diuretic" will also be tabulated.

(3) Table/figure number

Table 5.4-2

5.5 Occurrence of Adverse Events/Infections and Adverse Drug Reactions/Infections by Age Group

5.5.1 Occurrence of Adverse Events/Infections by Age Group

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of AE, etc. will be tabulated by age group (<65 years, 65 to 74 years, ≥75 years).

The type of AE, etc. will be tabulated as described in Section 5.1.

(3) Table/figure number

Table 5.5-1

5.5.2 Occurrence of Adverse Drug Reactions/Infections by Age Group

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by age group (<65 years, 65 to 74 years, ≥75 years).

The type of ADR, etc. will be tabulated as described in Section 5.1.

(3) Table/figure number

Table 5.5-2

5.6 Occurrence of Adverse Events/Infections and Adverse Drug Reactions/Infections by the Presence or Absence of Concurrent Hepatic Impairment

5.6.1 Occurrence of Adverse Events/Infections by the Presence or Absence of Concurrent Hepatic Impairment

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of AE, etc. will be tabulated by the presence or absence of concurrent hepatic impairment.

The type of AE, etc. will be tabulated as described in Section 5.1.

(3) Table/figure number

Table 5.6-1

5.6.2 Occurrence of Adverse Drug Reactions/Infections by the Presence or Absence of Concurrent Hepatic Impairment

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by the presence or absence of concurrent hepatic impairment.

The type of ADR, etc. will be tabulated as described in Section 5.1.

(3) Table/figure number

Table 5.6-2

5.7 Occurrence of Adverse Events/Infections and Adverse Drug Reactions/Infections by the Presence or

Absence of Concurrent Renal Impairment

5.7.1 Occurrence of Adverse Events/Infections by the Presence or Absence of Concurrent Renal Impairment

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of AE, etc. will be tabulated by the presence or absence of concurrent renal impairment.

The type of AE, etc. will be tabulated as described in Section 5.1.

(3) Table/figure number

Table 5.7-1

5.7.2 Occurrence of Adverse Drug Reactions/Infections by the Presence or Absence of Concurrent Renal Impairment

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by the presence or absence of concurrent renal impairment.

The type of ADR, etc. will be tabulated as described in Section 5.1.

(3) Table/figure number

Table 5.7-2

5.8 Occurrence of Adverse Drug Reactions/Infections by the Presence or Absence of Concomitant Antihypertensive Other than Zacras (during the Survey Period)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by the presence or absence of concomitant antihypertensive other than Zacras (during the survey period).

The type of ADR, etc. will be tabulated as described in Section 5.1.

A patient with “yes” for concomitant antihypertensive other than Zacras (during the survey period) and an ADR, etc. will be handled as a patient with “no” for concomitant antihypertensive other than Zacras if the ADR, etc. occurs before the start of concomitant treatment. A patient with “yes” for concomitant antihypertensive other than Zacras (during the survey period) and multiple ADRs, etc. will be handled as a patient with “yes” for concomitant antihypertensive other than Zacras if at least one ADR, etc. occurs after the start of concomitant treatment.

(3) Table/figure number

Table 5.8

5.9 Listing of Occurrence of Serious Adverse Events/Infections

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a SAE, etc.	Number of patients who experienced a SAE, etc.
Number of SAE, etc.	Number of reported SAE, etc. Multiple episodes of the same SAE, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of SAE, etc.	The incidence of SAE, etc. will be calculated as number of patients with a SAE, etc./number of patients included in safety evaluation × 100.
Type of SAE	SAEs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, SAEs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a SAE, etc. and the incidence of SAE, etc. will be listed by SOC internationally agreed order. For PT, the number and incidence of SAE, etc. will be listed in ascending order of PT code. Multiple episodes of the same SAE, etc. (PT) in the same patient will be tabulated as 1 patient/1 event. The number of SAE, etc. not related to Zacras will be presented in parentheses.

(3) Table/figure number

Table 5.9-1

5.10 Listing of Occurrence of Serious Adverse Events/Infections in Patients Excluded from Safety Evaluation

(1) Patients included in tabulation/analysis

Patients excluded from safety evaluation

(2) Data tabulated/analyzed

The following variables will be tabulated:

Variable	Data tabulated/analyzed
Number of patients with a SAE, etc.	Number of patients who experienced a SAE, etc.

Number of SAE, etc.	Number of reported SAE, etc. Multiple episodes of the same SAE, etc. (PT) in the same patient will be tabulated as the total number of episodes.
Incidence of SAE, etc.	The incidence of SAE, etc. will be calculated as number of patients with a SAE, etc./number of patients included in safety evaluation × 100.
Type of SAE	SAEs, etc. will be classified by SOC and then tabulated by PT. For laboratory tests, SAEs, etc. will be classified by SOC, then sorted by HLGT, and finally tabulated by PT. For SOC, the number of patients with a SAE, etc. and the incidence of SAE, etc. will be listed by SOC internationally agreed order. For PT, the number and incidence of SAE, etc. will be listed in ascending order of PT code. Multiple episodes of the same SAE, etc. (PT) in the same patient will be tabulated as 1 patient/1 event. The number of SAE, etc. not related to Zacras will be presented in parentheses.

(4) Table/figure number

Table 5.10-1

5.11 Changes in Test/Measurement Data over Time

5.11.1 Vital Signs (Pulse Rate)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation who have test data at 1 time point or more both before and after treatment with Zacras

(2) Data tabulated/analyzed

For pulse rate (bpm), summary statistics will be calculated for measured values at each time point of measurement [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics and 95% CI for the mean will be calculated, and the paired t-test will be performed.

(3) Table/figure number

Table 5.11-1

5.11.2 Laboratory Tests

(1) Patients included in tabulation/analysis

Patients included in safety evaluation who have test data at 1 time point or more both before and after treatment with Zacras

(2) Data tabulated/analyzed

For white blood cell count, platelet count, AST, ALT, γ-GTP, serum creatinine, BUN, and serum potassium, summary statistics will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics and 95% CI for the mean will be calculated.

(3) Table/figure number

Table 5.11-2

5.12 Occurrence of Adverse Drug Reactions/Infections by the Presence or Absence of Concomitant ACE Inhibitor (during the Survey Period)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by the presence or absence of concomitant ACE inhibitor.

The type of ADR, etc. will be tabulated as described in Section 5.1.

A patient with “yes” for concomitant ACE inhibitor (during the survey period) and an ADR, etc. will be handled as a patient with “no” for concomitant ACE inhibitor if the ADR, etc. occurs before the start of concomitant treatment. A patient with “yes” for concomitant

ACE inhibitor (during the survey period) and multiple ADRs, etc. will be handled as a patient with “yes” for concomitant ACE inhibitor if at least one ADR, etc. occurs after the start of concomitant treatment.

(3) Table/figure number

Table 5.12

5.13 Occurrence of Adverse Drug Reactions/Infections by the Presence or Absence of Concomitant Aldosterone Antagonist (during the Survey Period)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by the presence or absence of concomitant aldosterone antagonist.

The type of ADR, etc. will be tabulated as described in Section 5.1.

A patient with “yes” for concomitant aldosterone antagonist (during the survey period) and an ADR, etc. will be handled as a patient with “no” for concomitant aldosterone antagonist if the ADR, etc. occurs before the start of concomitant treatment. A patient with “yes” for concomitant aldosterone antagonist (during the survey period) and multiple ADRs, etc. will be handled as a patient with “yes” for concomitant aldosterone antagonist if at least one ADR, etc. occurs after the start of concomitant treatment.

(3) Table/figure number

Table 5.13

5.14 Occurrence of Adverse Drug Reactions/Infections by the Presence or Absence of Concomitant Renin Inhibitor (during the Survey Period)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by the presence or absence of concomitant renin inhibitor.

The type of ADR, etc. will be tabulated as described in Section 5.1.

A patient with “yes” for concomitant renin inhibitor (during the survey period) and an ADR, etc. will be handled as a patient with “no” for concomitant renin inhibitor if the ADR, etc. occurs before the start of concomitant treatment. A patient with “yes” for concomitant renin inhibitor (during the survey period) and multiple ADRs, etc. will be handled as a patient with “yes” for concomitant renin inhibitor if at least one ADR, etc. occurs after the start of

concomitant treatment.

(3) Table/figure number

Table 5.14

5.15 Occurrence of Adverse Drug Reactions/Infections by the Presence or Absence of Concomitant Diuretic (during the Survey Period)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by the presence or absence of concomitant diuretic.

The type of ADR, etc. will be tabulated as described in Section 5.1.

A patient with "yes" for concomitant diuretic (during the survey period) and an ADR, etc. will be handled as a patient with "no" for concomitant diuretic if the ADR, etc. occurs before the start of concomitant treatment. A patient with "yes" for concomitant diuretic (during the survey period) and multiple ADRs, etc. will be handled as a patient with "yes" for concomitant diuretic if at least one ADR, etc. occurs after the start of concomitant treatment.

(3) Table/figure number

Table 5.15

5.16 Occurrence of Adverse Drug Reactions/Infections by the Presence or Absence of Concomitant HCTZ (during the Survey Period)

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

The type of ADR, etc. will be tabulated by the presence or absence of concomitant HCTZ.

The type of ADR, etc. will be tabulated as described in Section 5.1.

A patient with "yes" for concomitant HCTZ (during the survey period) and an ADR, etc. will be handled as a patient with "no" for concomitant HCTZ if the ADR, etc. occurs before the start of concomitant treatment. A patient with "yes" for concomitant HCTZ (during the survey period) and multiple ADRs, etc. will be handled as a patient with "yes" for concomitant HCTZ if at least one ADR, etc. occurs after the start of concomitant treatment.

(3) Table/figure number

Table 5.16

6.0 Tabulation/Analysis of Efficacy

6.1 Changes in Blood Pressure over Time

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, summary statistics will be calculated for test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment]. For the change from the start of treatment with Zacras, summary statistics and 95% CI for the mean will be calculated, and the paired t-test will be performed. In addition, line graph with the mean ± standard deviation of test data on the vertical axis and the time point of test on the horizontal axis, and bar graph with the change on the vertical axis and the time point of test on the horizontal axis will be prepared. Paired t-test results will be displayed with an asterisk in graphs.

(3) Table/figure number

Table 6.1, Figure 6.1

6.2 Changes in Blood Pressure over Time <Male>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [sex: male] as described in Section 6.1.

(3) Table/figure number

Table 6.2, Figure 6.2

6.3 Changes in Blood Pressure over Time <Female>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [sex: female] as described in Section 6.1.

(3) Table/figure number

Table 6.3, Figure 6.3

6.4 Changes in Blood Pressure over Time <<65 Years>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [age: <65 years] as described in Section 6.1.

(3) Table/figure number

Table 6.4, Figure 6.4

6.5 Changes in Blood Pressure over Time <65 to 74 Years>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [age: 65 to 74 years] as described in Section 6.1.

(3) Table/figure number

Table 6.5, Figure 6.5

6.6 Changes in Blood Pressure over Time <≥75 Years>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [age: ≥75 years] as described in Section 6.1.

(3) Table/figure number

Table 6.6, Figure 6.6

6.7 Changes in Blood Pressure over Time <Presence or Absence of Concurrent Hepatic Impairment (No)>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [presence or absence of concurrent hepatic impairment: no] as described in Section 6.1.

(3) Table/figure number

Table 6.7, Figure 6.7

6.8 Changes in Blood Pressure over Time <Presence or Absence of Concurrent Hepatic Impairment (Yes)>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [presence or absence of concurrent hepatic impairment: yes] as described in Section 6.1.

(3) Table/figure number

Table 6.8, Figure 6.8

6.9 Changes in Blood Pressure over Time <Presence or Absence of Concurrent Renal Impairment (No)>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [presence or absence of concurrent renal impairment: no] as described in Section 6.1.

(3) Table/figure number

Table 6.9, Figure 6.9

6.10 Changes in Blood Pressure over Time <Presence or Absence of Concurrent Renal Impairment (Yes)>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of

treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [presence or absence of concurrent renal impairment: yes] as described in Section 6.1.

(3) Table/figure number

Table 6.10, Figure 6.10

6.11 Changes in Blood Pressure over Time <Concomitant Treatment with Zacras HD/HCTZ 6.25 mg (at the Start of Treatment with Zacras)>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [concomitant treatment with Zacras HD/HCTZ 6.25 mg (at the start of treatment with Zacras)] as described in Section 6.1.

(3) Table/figure number

Table 6.11, Figure 6.11

6.12 Changes in Blood Pressure over Time <Concomitant Treatment with Zacras HD/HCTZ 12.5 mg (at the Start of Treatment with Zacras)>

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

For systolic and diastolic blood pressure, test data at each time point of test [at the start of treatment with Zacras, from 1 to 12 months of treatment with Zacras, and at the final assessment] will be tabulated with the stratification factor [concomitant treatment with Zacras HD/HCTZ 12.5 mg (at the start of treatment with Zacras)] as described in Section 6.1.

(3) Table/figure number

Table 6.12, Figure 6.12

6.13 Proportion of Patients with Normal Blood Pressure

(1) Patients included in tabulation/analysis

Patients included in efficacy evaluation

(2) Data tabulated/analyzed

The proportion of patients with normal blood pressure at the start of the survey and the final assessment will be tabulated.

A patient with normal blood pressure is defined as a patient meeting both of the following criteria:

•Systolic blood pressure <140 mmHg

•Diastolic blood pressure <90 mmHg

(3) Table/figure number

Table 6.13

6.14 Factors that May Affect the Efficacy

(1) Patients included in tabulation/analysis

Patients included in safety evaluation

(2) Data tabulated/analyzed

For the changes in systolic and diastolic blood pressure at the final assessment, summary statistics and 95% CI for the mean will be calculated by the variables listed below, and the paired t-test will be performed.

Variable	Category
Sex	Male, female
Age	<65 years, ≥65 years
	<65 years, 65 to 74 years, ≥75 years
Predisposition to hypersensitivity	No, yes, unknown
Concurrent illness	No, yes
Disposition (multiple tabulation)	Diabetes, dyslipidemia, hyperuricemia, cardiac failure, coronary artery disease (myocardial infarction (including old myocardial infarction), angina, or other), atrial fibrillation, renal impairment (chronic kidney disease (CKD) [diabetic nephropathy, nephrosclerosis, or other] or other), hepatic impairment (hepatic steatosis, alcoholic hepatopathy, or other), cerebrovascular disorder
Medical history	No, yes, unknown
Body weight (kg)	<40, 40 to <50, 50 to <60, 60 to <70, ≥70, not measured
BMI (kg/m^2)	<18.5, 18.5 to <25.0, 25.0 to <30.0, ≥30.0, unknown
Initial dose of Zacras	LD, HD
Presence or absence of change in daily dose of Zacras	No, yes
Disposition (multiple tabulation)	LD → HD, HD → LD
Duration of treatment with Zacras	1 to 180 days, 181 to 360 days, ≥361 days The denominator is the number of patients treated with Zacras for 1

	day or more to calculate the incidence of AE, etc. for "1 to x days" and the number of patients treated with Zacras for x + 1 days or more to calculate the incidence of AE, etc. for "x + 1 to y days."
Treatment with antihypertensive other than Zacras (at the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Treatment with antihypertensive other than Zacras (during the survey period)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Treatment with antihypertensive other than Zacras (within 2 months before the start of treatment with Zacras)	No, yes
Disposition (multiple tabulation)*	ACE inhibitor, ARB, diuretic (thiazide and thiazide analogue diuretic), Ca antagonist, direct renin inhibitor, aldosterone antagonist, potassium-sparing diuretic, fixed-dose combination: ARB + diuretic, fixed-dose combination: ARB + Ca antagonist, fixed-dose combination: calcium antagonist + statin, other
Concomitant non-antihypertensive drug (during the survey period)	No, yes

Disposition (multiple tabulation)	Antidiabetic, antidyslipidemic, antihyperuricemic, other

* For fixed-dose combinations, individual ingredients will be tabulated separately. If “fixed-dose combination: ARB + diuretic” is used concomitantly, for instance, “ARB” and “diuretic” will also be tabulated.

(3) Table/figure number

Table 6.14