ERRATUM

Erratum to: Clinical Pharmacokinetics of Sacubitril/Valsartan (LCZ696): A Novel Angiotensin Receptor–Neprilysin Inhibitor

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Abstract Sacubitril/valsartan (LCZ696) is indicated for the treatment of heart failure with reduced ejection fraction. Absorption of sacubitril/valsartan and conversion of sacubitril (prodrug) to sacubitrilat (neprilysin inhibitor) was rapid with maximum plasma concentrations of sacubitril, sacubitrilat, and valsartan (angiotensin receptor blocker) reaching within 0.5, 1.5–2.0, and 2.0–3.0 h, respectively. With a twofold increase in dose, an increase in the area under the plasma concentration–time curve was proportional for sacubitril, ~1.9-fold for sacubitrilat, and ~1.7-fold for valsartan in healthy subjects. Following multiple twice-daily administration, steady-state maximum plasma concentration was reached within

3 days, showing no accumulation for sacubitril and valsartan, while ~1.6-fold accumulation for sacubitrilat. Sacubitril is eliminated predominantly as sacubitrilat through the kidney; valsartan is eliminated mainly by biliary route. Drug–drug interactions of sacubitril/valsartan were evaluated with medications commonly used in patients with heart failure including furosemide, warfarin, digoxin, carvedilol, levonorgestrel/ethinyl estradiol combination, amlodipine, omeprazole, hydrochlorothiazide, intravenous nitrates, metformin, statins, and sildenafil. Co-administration with sacubitril/valsartan increased the maximum plasma concentration (~2.0-fold) and area under the plasma concentration–time curve (1.3-fold) of atorvastatin; however, it did not affect the pharmacokinetics of simvastatin. Age, sex, or ethnicity did not affect the pharmacokinetics of sacubitril/valsartan. In patients with heart failure vs. healthy subjects, area under the plasma concentration–time curves of sacubitril, sacubitrilat, and valsartan were higher by approximately 1.6-, 2.1-, and 2.3-fold, respectively. Renal impairment had no significant impact on sacubitril and valsartan area under the plasma concentration–time curves, while the area under the plasma concentration–time curve of sacubitrilat correlated with degree of renal function (1.3-, 2.3-, 2.9-, and 3.3-fold with mild, moderate, and severe renal impairment, and end-stage renal disease, respectively). Moderate hepatic impairment increased the area under the plasma concentration–time curves of valsartan and sacubitrilat ~2.1-fold.

The in-text citations in the tables were misaligned with the references in the original article. The full article with all the corrections is republished here.

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Key Points

Sacubitril/valsartan is a first-in-class ARNI approved to reduce the risk of cardiovascular death and HF hospitalization in patients with HFrEF (NYHA II–IV).

No significant accumulation of either sacubitril or valsartan was observed at the steady state. The majority of sacubitril (primarily as sacubitrilat) is excreted in urine and a majority of valsartan is excreted in feces.

No clinically relevant interactions were observed when sacubitril/valsartan was coadministered with digoxin, warfarin, HCTZ, amlodipine, omeprazole, metformin, carvedilol or a combination oral contraceptive.

Caution should be exercised when administering sacubitril/valsartan with statins, considering the ~twofold increase in the $C_{\max}$ of atorvastatin (with no impact on AUC).

The AUC of sacubitrilat increased with increasing severity of renal impairment with no impact in patients with mild renal impairment and a 2.3, 2.9, and 3.3-fold higher in patients with moderate- and severe renal impairment, and end state renal disease without dialysis, respectively, compared with healthy subjects.

In patients with hepatic impairment, increases in the AUC and $C_{\max}$ of sacubitril were not considered clinically relevant because it is an inactive prodrug, while the observed increase in the AUC of valsartan was consistent with its route of elimination.

1 Introduction

Chronic heart failure (HF) poses a significant global health burden with an estimated prevalence of 1–2% of adult populations of developed countries [1, 2]. Neurohormonal pathways such as the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system play a critical role in the pathophysiology of HF, with initial compensatory and subsequent detrimental actions. Inhibition of RAAS with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in combination with β -blockers and mineralocorticoid receptor antagonists are established treatments for chronic HF [3–9]. However, despite the considerable therapeutic advances in the treatment of HF in the past two decades, the 5-year mortality of HF remains (50%) [10].

Natriuretic peptides (NPs), through activation of membrane-bound NP receptors and their second messenger cyclic guanosine monophosphate (cGMP), mediate beneficial cardio-renal effects such as natriuresis, diuresis, vasodilatation, inhibition of RAAS, sympathetic nervous system, and aldosterone secretion [11]. Despite their upregulation in HF, NPs do not fully compensate the activation of RAAS and sympathetic nervous system, potentially owing to a deficiency of biologically active peptides [12–14]. Enhancing the biological activity of NPs, particularly in conjunction with RAAS blockade can provide therapeutic benefits [15]. Angiotensin receptor–neprilysin inhibition is a novel therapeutic concept based on enhancing the availability of biologically active NPs by inhibiting their degradation by neprilysin, while simultaneously blocking the deleterious effects of sustained RAAS activation [16].

Sacubitril/valsartan (LCZ696), a first-in-class angiotensin receptor–neprilysin inhibitor, provides simultaneous neprilysin inhibition and angiotensin receptor blockade. Compared with enalapril, in patients with HF and reduced ejection fraction (HFrEF), treatment with sacubitril/valsartan resulted in a superior reduction in the risk of cardiovascular death (20%), HF hospitalization (20%), and death from any cause (16%) and provided other benefits [17, 18]. Considering these beneficial effects, sacubitril/valsartan has been approved in >60 countries for the treatment of HFrEF and is recommended by European and American HF guidelines [1, 19] for the treatment of chronic symptomatic HFrEF (New York Heart Association Class II–IV). The beneficial effects of sacubitril/valsartan on clinical outcomes are currently being studied in patients with HF and preserved ejection fraction (HFpEF; PARAGON-HF trial; Clinical Trial Registry: NCT01920711) [20]; in post-myocardial infarction (PARADISE-MI trial; Clinical Trial Registry: NCT02678312); and in pediatric patients with HFrEF (Clinical Trial Registry: NCT02678312). The present review summarizes the clinical pharmacokinetics of sacubitril/valsartan following oral single- and multiple-dose administrations in healthy subjects and in patients with HF. Furthermore, the drug–drug interaction potential and the impact of age, sex, race, ethnicity, and renal or hepatic impairment on the pharmacokinetics of sacubitril/valsartan are described.

2 Physicochemical Properties of Sacubitril/Valsartan

Sacubitril/valsartan is a sodium salt complex of anionic forms of sacubitril (an inactive prodrug of the active neprilysin inhibitor, sacubitrilat) and valsartan (an angiotensin receptor blocker) in a 1:1 molar ratio [21, 22]. The

sacubitril/valsartan 50-mg dose contains 24 mg of sacubitril and 26 mg of valsartan; the 100-mg dose contains 49 mg of sacubitril and 51 mg of valsartan, and the 200-mg dose contains 97 mg of sacubitril and 103 mg of valsartan. Upon oral administration, sacubitril/valsartan provides systemic exposure to sacubitril, sacubitrilat, and valsartan.

Sacubitril/valsartan is highly soluble in water (100 mg/mL) [23]. In-vitro permeability assays using Caco-2 cell monolayers showed a moderate-to-high permeability of sacubitril with an effective permeability coefficient of $>50 \times 10^{-5}$ cm/min [24]. Sacubitril exhibits P-glycoprotein (P-gp)-mediated efflux [25]. Although no study has been conducted to determine the impact of P-gp inhibition on the bioavailability of sacubitril, the impact is expected to be minimal considering high permeability and bioavailability ($>60\%$) of sacubitril. Valsartan is categorized as a class III drug according to the biopharmaceutical classification system, known to exhibit low permeability, high solubility, and poor metabolism [26].

3 Clinical Pharmacokinetics

3.1 Single- and Multiple-Dose Pharmacokinetics in Healthy Subjects

Pharmacokinetic data of sacubitril/valsartan following administration of single ascending doses of 5–1200 mg were pooled from 11 clinical pharmacology studies conducted in healthy adults (Table 1). Following oral administration, sacubitril and valsartan were rapidly absorbed reaching maximum plasma concentration ($C_{\max}$) within the median time [time to maximum plasma concentration ($T_{\max}$); range represents data from different studies] of 0.5 and 1.5–2.0 h, respectively. The conversion of sacubitril to sacubitrilat was also rapid, with a median $T_{\max}$ of 2.0–3.0 h for sacubitrilat. Increasing dose did not impact the $T_{\max}$ of all analytes. A pooled analysis of single-dose pharmacokinetics following administration of 200 and 400 mg of sacubitril/valsartan (representative doses) is presented in Table 2 and the representative area under the plasma concentration–time curves (AUCs) are presented in Fig. 1. With twofold increase in the dose within the evaluated dose range, the increase in the AUC was dose proportional for sacubitril, ~ 1.9 -fold for sacubitrilat, and ~ 1.7 -fold for valsartan. Following single-dose administration, the absolute oral bioavailability was estimated as 60% for sacubitril [27]. The absolute oral bioavailability of valsartan delivered by sacubitril/valsartan was approximately 60% higher than the 23% bioavailability reported for other marketed formulations of valsartan when administered alone [27, 28]. The 200-mg dose of sacubitril/valsartan containing 103 mg of valsartan provided systemic exposure of

valsartan similar to that following administration of 160 mg of valsartan in alternate marketed formulations. The single ascending dose pharmacokinetics of sacubitril/valsartan in healthy subjects from this pooled analysis is consistent with previously reported pharmacokinetic data [21].

Upon multiple-dose administration, all analytes of sacubitril/valsartan reached steady-state plasma concentrations within 3 days of once-daily (QD) or twice-daily (BID) administration [25, 29]. The steady-state pharmacokinetic assessments of sacubitril/valsartan (50–900 mg QD) showed a rapid absorption of sacubitril and valsartan similar to single-dose administrations with a $T_{\max}$ of 0.6–0.9 and 1.6–4.9 h, respectively [21]. In addition, sacubitrilat levels increased rapidly with a $T_{\max}$ of 1.8–2.7 h, suggesting rapid conversion of sacubitril. No significant accumulation of either sacubitril or valsartan was observed at any dose level of sacubitril/valsartan following QD administration. Minimal accumulation of sacubitrilat ($R = 1.2$) was observed in all dose groups of sacubitril/valsartan. The inter-subject variability (coefficient of variation) of pharmacokinetic parameters was estimated to be 20–39% for sacubitril, 11–26% for sacubitrilat, and 17–58% for valsartan [21].

The accumulation of analytes of sacubitril/valsartan following multiple twice-daily administration of the 200-mg dose pooled from five studies (Table 2) was consistent with that reported in a previous study [29], wherein no significant accumulation of sacubitril and valsartan (1.3-fold) was observed, while a 1.6-fold accumulation was observed for sacubitrilat.

3.2 Effect of Food

The effect of food on the pharmacokinetics of all the analytes (Table 3) was evaluated in healthy subjects following administrations of sacubitril/valsartan 400 mg with a low-fat meal (500–600 kcal) and a high-fat meal (800–1000 kcal) [24] and 200 mg of sacubitril/valsartan with a Japanese meal (~ 500 kcal, 14% fat) [30]. Administration of sacubitril/valsartan with food resulted in a decreased rate of absorption of sacubitril, as indicated by a delayed $T_{\max}$ (by 1–2 h) and a decreased $C_{\max}$ (by 48–72%). Consequently, the rate of appearance of its active metabolite sacubitrilat in plasma was delayed and the $C_{\max}$ was decreased (by 19–28%). However, no marked changes were observed in the AUC of sacubitrilat, indicating no clinical relevance of the decreased $C_{\max}$ of sacubitril (in-active prodrug) under fed conditions. Conversely, for valsartan, a significant decrease was observed in the $C_{\max}$ (by 39–51%) and AUC (by 34–40%; except when administered with a high-fat meals, which resulted in only a 9% decrease); these

Table 1 Summary of clinical trials conducted to study pharmacokinetics of sacubitril/valsartan

References	N	Objective	Dose/frequency	Population
Single dose pharmacokinetics of sacubitril/valsartan 5–1200 mg dose range in healthy subjects				
Akahori et al. [30] ^a	40	Single ascending dose study assessing safety and tolerability and PK of sacubitril/valsartan	Single doses Sacubitril/valsartan 20, 80, 200, 400, and 600 mg Placebo	Healthy subjects (Japanese)
Gu et al. [21]	25	Single ascending dose assessing PK, safety and tolerability of sacubitril/valsartan vs valsartan	Single doses Sacubitril/valsartan 5, 20, 80 mg Valsartan 40 mg	Healthy subjects
Gu et al. [21] ^a	65	Single and multiple ascending dose study assessing safety and tolerability; PK and PD of sacubitril/valsartan	Single doses Sacubitril/valsartan 200, 600, 900, and 1200 mg Multiple doses Sacubitril/valsartan 50, 200, 600, and 900 mg QD for 14 days Placebo	Healthy subjects
Gu et al. [21]	53	Relative bioavailability of valsartan from sacubitril/valsartan versus valsartan marketed formulation	Single doses Sacubitril/valsartan 400 mg Valsartan 320 mg	Healthy subjects
Ayalasomayajula et al. [24]	36	Effect of food on the PK of sacubitril/valsartan	Single dose Sacubitril/valsartan 400 mg	Healthy subjects
Gan et al. [94]	36	Effect of age and gender on sacubitril/valsartan	Single dose Sacubitril/valsartan 400 mg	Healthy subjects
Gan et al. [49]	28	PK interaction with omeprazole	Multiple doses once-daily Sacubitril/valsartan 400 mg Omeprazole 40 mg	Healthy subjects
Han et al. [100] ^a	40	Single ascending dose study of sacubitril/valsartan in Chinese population	Single doses Sacubitril/valsartan 50, 100, 200, 400 mg	Healthy subjects (Chinese)
Langenickel et al. [101]	83	Thorough QTc study	Single doses Sacubitril/valsartan 400 and 1200 mg; moxifloxacin 400 mg; placebo	Healthy subjects
CLCZ696B2126 ^a	40	Relative bioavailability of sacubitril/valsartan minitables and effect of food on the PK of sacubitril/valsartan minitables	Single doses Sacubitril/valsartan 200 mg FMI and minitables	Healthy subjects
Kulmatycki et al. [45] ^a	32	Effect of hepatic impairment on sacubitril/valsartan PK	Single dose Sacubitril/valsartan 200 mg	Patients with mild/moderate hepatic impairment and matched healthy subjects
Steady-state pharmacokinetics of sacubitril valsartan 200 mg BID and 400 mg QD in healthy subjects				
Ayalasomayajula et al. [29]	28	PK interaction with atorvastatin	Multiple doses Sacubitril/valsartan 200 mg BID Atorvastatin 80 mg QD	Healthy Chinese subjects
Ayalasomayajula et al. (Submitted)	28	PK and PD interaction with furosemide	Multiple doses of sacubitril/valsartan 200 mg BID Single dose of furosemide 40 mg	Healthy subjects
Ayalasomayajula et al. [25]	24	PK interaction with digoxin	Multiple doses Sacubitril/valsartan 200 mg BID Digoxin 0.25 mg QD	Healthy subjects

Table 1 continued

References	N	Objective	Dose/frequency	Population
Ayalasomayajula et al. [25]	25	PK and PD interactions with warfarin	Multiple doses of sacubitril/valsartan 200 mg BID Single dose Warfarin sodium 25 mg	Healthy subjects
Schuehly et al. (submitted; EudraCT no. 2013-001783-36)	39	PD interaction with intravenous nitroglycerin	Multiple doses of sacubitril/valsartan 200 mg BID Nitroglycerin infusion up to 40 µg/min matching placebo	Healthy subjects
Hsiao et al. [48] ^b	28	PK interaction with amlodipine	Multiple once daily doses Sacubitril/valsartan 400 mg Amlodipine 10 mg	Healthy subjects
Impact of body weight and BMI on pharmacokinetics of sacubitril/valsartan in healthy subjects^b				
Gan et al. [49]	26	PK interaction with metformin	Multiple once daily doses Sacubitril/valsartan 400 mg Metformin 1000 mg	Healthy Japanese subjects
Hsiao et al. [48]	28	PK interaction with carvedilol	Multiple doses Sacubitril/valsartan 400 mg QD Carvedilol 12.5 and 25 mg (titration) BID	Healthy subjects
Hsiao et al. [48]	28	PK interaction with HCTZ	Multiple once daily doses Sacubitril/valsartan 400 mg HCTZ 25 mg	Healthy subjects
Pharmacokinetics of sacubitril/valsartan in patients				
Kobalava et al. [38]	30	Multiple dose study assessing safety, tolerability, PK and PD of sacubitril/valsartan	Sacubitril/valsartan 7-day dose titration with 100 mg bid followed by 200 mg bid for 14 days (optional start of dose titration with sacubitril 50 mg was not utilized)	Patients with stable CHF (NYHA II-IV)
NCT01353508	16	Effect of sacubitril/valsartan versus valsartan on natriuresis in patients with HF and hypertension	Multiple once daily doses Sacubitril/valsartan 400 mg Valsartan 320 mg	Patient with stable CHF
Regression analysis of impact of body weight on pharmacokinetics of sacubitril/valsartan				
Ito et al. [93]	32	Safety, tolerability and efficacy of sacubitril/valsartan in Japanese hypertensive patients with renal dysfunction	Multiple once daily doses Sacubitril/valsartan 100, 200 and 400 mg Placebo	Japanese hypertensive patients with renal dysfunction
Rakugi et al. [92]	387	Efficacy and safety of sacubitril/valsartan compared to olmesartan in Japanese patients with essential hypertension	Sacubitril/valsartan 200 mg QD for 1 week, up-titrated to 400 mg QD for 7 weeks Olmesartan 20 mg QD for 8 weeks Placebo	Japanese patients with mild-to-moderate essential hypertension

BID twice daily, *BMI* body mass index, *HCTZ* hydrochlorothiazide, *PD* pharmacodynamics, *PK* pharmacokinetics, *QD* once daily

^a Studies included in analyzing the impact of race and ethnicity

^b Hsiao et al. [48] (included in single ascending dose pharmacokinetics) is also included in analyzing the impact of body weight

changes in exposure (AUC) to valsartan in the presence of food are consistent with previous reports, wherein the pharmacokinetics of valsartan was similar under fed and fasting conditions [31, 32]. In addition, efficacy and safety were established in the phase III PARADIGM-HF trial [17], wherein sacubitril/valsartan was administered

regardless of food intake. Overall, the effect of food on the pharmacokinetics of sacubitril/valsartan is consistent irrespective of the doses (200 or 400 mg) administered, and food intake is not expected to alter its pharmacodynamics. Therefore, sacubitril/valsartan can be administered without regard to meals.

Table 2 Pharmacokinetics of sacubitril, sacubitril/valsartan following administration of sacubitril/valsartan 400 mg QD and 200 mg BID at steady state in healthy subjects and in patients with HF

N	Sacubitril/valsartan single dose		Sacubitril/valsartan multiple dose		Heart failure	
	400 mg	200 mg	400 mg QD	200 mg BID		
	Healthy subjects					
			26	144	43	
Sacubitril	AUC (ng* ^a h/mL)	4424.1 (1504)	2054.2 (566)	3600 (992)	2113.8 (724)	3253 (1252); CV%, 38
	C _{max,ss} (ng/mL)	3280.7 (1686)	1919.7 (968)	3010 (1180)	1793.8 (978)	2421.4 (1299); CV%, 53
	T _{max} (h) ^a	0.5 (0.48–4.0)	0.5 (0.5–4.0)	1.0 (0.5–4.0)	0.5 (0.5–4.0)	0.5 (0.5–2.0)
	T _{1/2} (h)	1.5 (0.6)	1.4 (0.6)			3.9 (3.6); CV%, 92
	CL/F (L/h)	54.9 (18.5)	51.1 (14.6)		73.6 (34.2)	36.2 (14.6); CV%, 40
	AUC (ng* ^a h/mL)	153,422.7 (37,956)	81,050.1 (16,843)	148,000 (27,900)	73,623.6 (21,050); CV%, 29	151,611 (50024); CV%, 33
Sacubitrilat	C _{max,ss} (ng/mL)	14,605.0 (3545)	8086.2 (1618)	16,500 (3080)	10,616.5 (2781); CV%, 26	16,530.5 (4359); CV%, 26
	T _{max} (h) ^a	2.1 (1.0–6.0)	2.0 (1.0–6.0)	3.0 (1.0–6.0)	2 (1.0–6.0)	2 (1.0–6.0)
	T _{1/2} (h)	10.3 (2.7)	11.5 (2.5)		6.7 (1.7); CV%, 25	18.4 (6.8); CV%, 37
	AUC (ng* ^a h/mL)	35,387.8 (14,928)	22,291.7 (8622)	32,200 (11,500)	18,795 (9098); CV%, 48	41,387.7 (19,597); CV%, 47
Valsartan	C _{max,ss} (ng/mL)	5302.6 (2215)	3969.8 (1428)	5580 (2090)	3825.2 (1723); CV%, 45	6154.2 (2461); CV%, 40
	T _{max} (h) ^a	2.0 (1.0–5.1)	1.5 (1.0–4.0)	1.5 (1.0–3.0)	1.5 (1–4)	2 (1–4)
	T _{1/2} (h)	10.9 (12.6)	9.9 (5.1)		4.9 (1.8); CV%, 37	13.7 (5.0); CV%, 37
	CL/F (L/h)		5.4 (2.7)		9.7 (5.3); CV%, 54	3.1 (1.1); CV%, 35

Single-dose pharmacokinetics: data of sacubitril/valsartan 200 mg were pooled from five studies in healthy subjects [21, 30, 45, 100]; data on file for furosemide study (CLCZ696B2126) study] and data of sacubitril/valsartan 400 mg data were pooled from seven studies [21, 24, 30, 49, 94, 100, 101]. Steady-state representative pharmacokinetics: data of sacubitril/valsartan 400 mg QD in healthy subjects was reported by Gan et al. [49]; data of sacubitril/valsartan 200 mg in healthy subjects data were pooled from five studies [25, 29] (data on file for two studies including DDI study with furosemide and nitroglycerine, EudraCT no. 2013-001783-36; refer to Table 1); data of sacubitril/valsartan 200 mg BID in patients with HF data were pooled from two studies [38] (data on file for 1 study; CLCZ696B2223, clinical trial registry number: NCT01353508; refer to Table 1). Data are presented as mean (standard deviation)

AUC area under the plasma concentration–time curve from time, BID twice daily, CL/F apparent systemic (or total body) clearance from plasma following extravascular administration, C_{max,ss} maximum observed plasma drug concentration after drug administration at steady state, h hours, HF heart failure, QD once daily, T_{1/2} the elimination half-life associated with the terminal slope of a semilogarithmic concentration–time curve, T_{max} time to achieve maximum concentration following drug administration

^a Data for T_{max} are median (range); area under the plasma concentration–time curve from time zero to infinity for single doses and area under the plasma concentration–time curve for a dosing interval for multiple doses

Fig. 1 Single- and multiple-dose pharmacokinetic profiles of sacubitril, sacubitrilat, and valsartan in healthy subjects following administration of sacubitril/valsartan. *BID* twice daily, *QD* once daily, *SD* single dose

3.3 Distribution and Protein Binding

Human plasma protein binding was characterized in vitro for sacubitril, sacubitrilat, and valsartan. Over a concentration range of 0.02–100 $\mu\text{g/mL}$, protein binding for both sacubitril and sacubitrilat was 97% [27]. Protein binding of valsartan was also high (96%) in human serum at concentrations ranging from 0.05 to 5 $\mu\text{g/mL}$ [33]. Sacubitrilat crosses the blood–brain barrier to a very limited extent (0.28%) [34]. The average apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively [27].

3.4 Metabolism

Sacubitril/valsartan analytes do not undergo significant metabolism by cytochrome P450 (CYP) isozymes; sacubitril undergoes ester hydrolysis to form sacubitrilat, which is the primary metabolite of sacubitril ($\sim 76.8\%$ of total exposure following oral dose of sacubitril/valsartan) [22]. The ester hydrolysis of sacubitril is primarily mediated via carboxylesterase 1, but not carboxylesterase 2 [35]. The role of other carboxylesterases remains unknown. Valsartan is minimally metabolized with approximately 20% of the dose recovered as metabolites. Valsartan undergoes

Table 3 Effect of food on systemic exposure of sacubitrilat and valsartan following single-dose administration of sacubitril/valsartan

	Sacubitril/valsartan 400 mg		Sacubitril/valsartan 200 mg
	Low fat	High fat	Japanese meal
Sacubitrilat			
AUC_{inf}	0.84 (0.72–0.95)	1.00 (0.86–1.15)	0.79 (0.68–0.93)
AUC_{last}	0.84 (0.73–0.95)	1.05 (0.92–1.19)	0.79 (0.67–0.93)
C_{max}	0.52 (0.42–0.64)	0.44 (0.35–0.53)	0.28 (0.20–0.41)
Sacubitril			
AUC_{inf}	1.0 (0.97–1.02)	1.04 (1.01–1.06)	0.92 (0.90–0.95)
AUC_{last}	0.91 (0.8–1.03)	1.04 (0.92–1.18)	0.92 (0.90–0.95)
C_{max}	0.81 (0.7–0.92)	0.72 (0.63–0.82)	0.73 (0.70–0.77)
Valsartan			
AUC_{inf}	0.66 (0.57–0.75)	0.91 (0.79–1.04)	0.60 (0.45–0.81)
AUC_{last}	0.67 (0.58–0.76)	0.91 (0.79–1.04)	0.60 (0.45–0.81)
C_{max}	0.61 (0.51–0.71)	0.6 (0.51–0.70)	0.49 (0.33–0.73)

Data are presented as geometric mean ratio (90% CI) for test (fed)/reference (fasted)

AUC_{inf} area under the plasma concentration–time curve from time zero to infinity, AUC_{last} area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration, CI confidence interval, C_{max} maximum plasma concentration

CYP2C9-mediated metabolism to form the minor metabolite (9%) valeryl 4-hydroxy valsartan [36, 37].

3.5 Elimination

The apparent clearance (CL/F) of sacubitril and valsartan are 51.1 and 5.4 L/h (Table 2), with an estimated half-life of approximately 1.4, 11.5, and 9.9 h, for sacubitril, sacubitrilat, and valsartan, respectively, in healthy subjects [27]. Following oral administration, approximately 52–68% of sacubitril (primarily as sacubitrilat) and approximately 13% of valsartan and its metabolites are excreted in urine; 37–48% of sacubitril (primarily as sacubitrilat), and 86% of valsartan and its metabolites are excreted in feces. Unchanged sacubitril accounts for 0.8–2.8% of the dose in urine and 0.3–0.9% of the dose in feces [22, 27].

4 Pharmacokinetics in Patients with Heart Failure

In an open-label study in patients with HFrEF, the target patient population, plasma concentrations of all analytes increased rapidly following multiple doses of sacubitril/valsartan (100 mg BID for 7 days and 200 mg BID for 14 days) [38] with a steady-state median T_{max} similar to that observed in healthy subjects [25]. The steady-state AUC of sacubitril/valsartan at the 100- and 200-mg BID doses appeared to be dose proportional for both sacubitril and sacubitrilat, and less than dose proportional for valsartan [38].

The pooled analysis of steady-state pharmacokinetics of sacubitril/valsartan 200 mg BID in patients with HFrEF (pooled from two studies) compared with data from healthy subjects (pooled from five studies) are presented in Table 2. The AUCs of sacubitril, sacubitrilat, and valsartan were higher by approximately 1.6-, 2.1-, and 2.3-fold, respectively, in patients with HFrEF compared with healthy subjects, which could be because of reduced clearance potentially owing to altered hepatic and/or renal function in patients with HF [39–41]. Similarly, it was earlier reported that the steady-state AUC and C_{max} of valsartan 160 mg BID observed in patients with HFrEF [42] were approximately 1.3–2.0 times higher than those observed in healthy subjects [43]. The CL/F of sacubitril and valsartan was reduced by approximately 2.0- and 3.0-fold, respectively, in patients with HF compared with that observed in healthy subjects. The CL/F of sacubitrilat was not determined as it is the active metabolite formed from sacubitril.

Additional information in patients with HFrEF is available from the PARADIGM-HF trial cohort where 311 patients underwent sparse pharmacokinetic sampling (data on file), the data of which were compared with the pooled data from subjects without HFrEF ($n = 38$) in three clinical pharmacology studies [44, 45]. The CL/F of valsartan (5.4 vs. 3.3 L/h), sacubitril (54.8 vs. 37.1 L/h), and sacubitrilat (0.7 vs. 0.4 L/h) in patients with HFrEF was approximately two-times lower than that observed in subjects without HFrEF (pooled data from three clinical pharmacology studies) [44, 45]. The estimated half-life in patients with HFrEF was comparable but slightly higher to that observed in subjects without HFrEF for valsartan

(13.6 h) and sacubitril (6.0 h); however, ~50% greater for sacubitrilat (13.0 h). The predicted accumulation in patients with HFrEF appeared to be ~twofold higher than that observed in subjects without HFrEF for valsartan (1.9 vs. 1.2) and sacubitrilat (3.3 vs. 1.7); whereas no appreciable accumulation of sacubitril was observed in either population. The mean absorption rate for patients with HFrEF compared with subjects without HFrEF was approximately twofold lower for valsartan (0.16 ± 0.07 vs. 0.29 ± 0.07 per hour), whereas no difference was observed for sacubitril (1.35 ± 0.09 vs. 1.34 ± 0.15 per hour). Exposure to sacubitril/valsartan observed in the PARADIGM-HF trial using sparse pharmacokinetic sampling is comparable to that observed in the study with intense pharmacokinetic sampling [38].

5 Drug–Drug Interactions

Heart failure guidelines recommend the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, and aldosterone antagonists for the treatment of HFrEF [1, 46]. In addition, several patients are being treated with diuretics, digoxin, warfarin, and other medications (e.g., anti-hypertensive agents and lipid-lowering drugs) related to prevalent co-morbidities. Sacubitril/valsartan was assessed for potential pharmacokinetic or pharmacodynamic drug–drug interactions that could result in differences in the exposure or response to treatment.

Metabolism of sacubitril, sacubitrilat, and valsartan by CYP450 enzymes is minimal and inhibition/induction potential of CYP450 enzymes by sacubitril, sacubitrilat, and valsartan is low. Both sacubitrilat and valsartan are weak inhibitors of CYP2C9. Therefore, pharmacokinetic drug–drug interactions with inhibitors, inducers, or substrates of CYP450 enzymes are unlikely. In-vitro inhibition of organic anion transporter protein (OATP) 1B1 [half-maximal inhibitory concentration (IC₅₀), 1.9 μ M], OATP1B3 (IC₅₀, 3.8 μ M) [47], and OAT3 (IC₅₀, 0.8 μ M) by sacubitril was observed at clinically relevant concentrations. Sacubitrilat and valsartan were found to be a substrate of OAT3 in vitro; however, a clinically relevant drug–drug interaction at therapeutic doses is unlikely to happen (data on file). Sacubitril is a P-gp substrate. Although no study has been conducted to determine the impact of P-gp inhibition on the bioavailability of sacubitril, the impact is expected to be minimal considering high permeability and bioavailability (>60%) of sacubitril.

A total of 13 clinical pharmacology studies were conducted to evaluate the pharmacokinetic and/or pharmacodynamic drug–drug interaction potential with medicines that may be co-administered with sacubitril/valsartan in patients with HFrEF [25, 29, 47–49]. The mechanistic

pharmacokinetic drug interaction potential of sacubitril/valsartan was evaluated with CYP3A4, CYP2C9, CYP2C19, CYP2D6, and other CYP enzyme substrates (carvedilol, omeprazole, warfarin, and amlodipine); P-gp (digoxin); OATP1B1/OATP1B3 (atorvastatin and simvastatin); and OAT3 (furosemide). In addition, the pharmacokinetic and pharmacodynamic interaction potential with nitroglycerine and sildenafil was also evaluated because the pharmacodynamic actions are mediated through a common second messenger, cGMP. The pharmacokinetic drug–drug interaction potential was also evaluated with other common co-medications such as antidiabetic agents (metformin), antihypertensive agents (hydrochlorothiazide, HCTZ), and a combination of oral contraceptives (COCs). The effects of co-administration on the pharmacokinetics of either sacubitril/valsartan or the concomitant medication is presented in Fig. 2.

5.1 Carvedilol

Carvedilol, a non-selective β -blocker and a substrate for CYP2C9, CYP2D6, and P-gp [50–52], demonstrated efficacy in reducing the risk of death in patients with HFrEF [3, 53] and may thus be co-administered with sacubitril/valsartan. Co-administration of sacubitril/valsartan (400 mg QD) for 5 days showed no impact on steady-state pharmacokinetics of both R(+)- and S(–)-carvedilol enantiomers in healthy subjects [48]. While steady-state pharmacokinetics of sacubitrilat remained unchanged, the AUC and C_{max} of valsartan decreased marginally by 12 and 9%, respectively [48]. This is not considered to be clinically relevant as the observed changes were smaller than the intra-individual variability. These results support the lack of inhibition of aforementioned CYP enzymes by sacubitril/valsartan analytes.

5.2 Omeprazole

Omeprazole, a proton pump inhibitor and a substrate of CYP3A4 and CYP2C19, is widely used for the treatment of gastric acid-related disorders in patients with different diseases including cardiovascular disease [54–56]. An increase in gastric pH following administration of omeprazole can interfere with the absorption of co-medications with pH-dependent solubility [55]. Because the solubility of valsartan and sacubitril (weak acids) is higher at higher pH conditions, the dissolution rate is also expected to be higher. Therefore, a potential for increased bioavailability of sacubitril/valsartan exists when co-administered with omeprazole. Following administration of omeprazole (40 mg QD) for 5 days in healthy subjects and co-administration of single-dose sacubitril/valsartan 400 mg on day 5, the T_{max} of all three sacubitril/valsartan

Fig. 2 Drug–drug interactions between sacubitril/valsartan and co-administered medicines. Effect of co-administered medicines on area under the plasma concentration–time curve (AUC) (**a**) and maximum plasma concentration (C_{max}) (**b**) of analytes of sacubitril/valsartan;

and the effect of sacubitril/valsartan on AUC (**c**) and C_{max} (**d**) of co-administered medicines. *EES* ethinyl estradiol, *HCTZ* hydrochlorothiazide, *LVG* levonorgestrel, *OC* oral contraceptive

analytes remained unchanged [49]. The AUC remained unchanged [as 90% confidence interval (CI) were within 0.8–0.12], while the marginal decrease in C_{max} of sacubitril was decreased by 7% and is considered not to be clinical relevant [49]. This is because the lower bound of 90% CI of C_{max} of sacubitril (0.77) was only slightly lower than 0.8, but still within the high inter-subject variability of C_{max} (>70%) of sacubitril [49]. For sacubitrilat, co-administration did not affect any pharmacokinetic parameter, whereas a marginal decrease in AUC_{inf} and C_{max} (by 11 and 13%, respectively) was observed for valsartan [49]. However, it should be noted that valsartan typically shows high

variability (>40%) in its pharmacokinetic parameters [57]. Co-administration of sacubitril/valsartan with omeprazole was not associated with clinically relevant pharmacokinetic drug interactions.

5.3 Warfarin

Warfarin, a vitamin K antagonist, is a widely used anti-coagulant for the long-term prevention of thrombosis [58]. Minor changes in pharmacokinetic exposure to warfarin may have considerable impact on its safety and efficacy owing to its narrow therapeutic index. Metabolism is

primarily by CYP2C9 for *S*(-)-warfarin and by CYP1A2, CYP3A4, and CYP2C19 for *R*(+)-warfarin [59, 60]. Therefore, co-administration with CYP inhibitors can increase the concentration of warfarin enantiomers, thereby increasing the anticoagulant effect and risk of bleeding [61]. An in vitro study identified a weak inhibition of CYP2C19 by sacubitril (IC₅₀, ~20 µM) and of CYP2C9 by sacubitrilat (IC₅₀, ~40 µM) [22]. However, administration of a single 25-mg dose of warfarin on day 5 of sacubitril/valsartan 200 mg BID in healthy subjects did not impact the pharmacokinetics of *R*(+)- and *S*(-)-warfarin enantiomers as the geometric mean ratio (GMR) and corresponding 90% CIs were within the 0.8–1.25 range for both C_{max} and AUC [25]. Consistent with the lack of a pharmacokinetic interaction, no pharmacodynamic interaction was evidenced by unchanged prothrombin time and International Normalized Ratio values following co-administration of sacubitril/valsartan and warfarin. Moreover, warfarin had no effect on the steady-state pharmacokinetics of sacubitril/valsartan.

5.4 Statins

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme reductase (statins) are the first-line pharmacological treatment for hypercholesterolemia [62, 63]. Statin therapy reduces the risk of acute coronary syndromes, coronary procedures, and other coronary outcomes in both primary and secondary prevention [62, 63]. In the recently reported PARADIGM-HF trial, about 56% of patients were receiving statins [64]. Statins are eliminated via CYP-mediated metabolism and/or biliary excretion following hepatic uptake mediated by OATPs, particularly OATP1B1 and OATP1B3 [65, 66]. Organic anion transporter proteins are important molecular targets for transporter-mediated drug–drug interactions, and several such interactions have been reported with statins [67–69]. More importantly, co-administration with CYP and OATP1B1/1B3 inhibitors could increase the exposure to statins, thereby increasing the risk of statin-related adverse events including myopathy and rhabdomyolysis [70].

In-vitro inhibition of OATP1B1 (IC₅₀, 1.9 µM) and OATP1B3 (IC₅₀, 3.8 µM) by sacubitril indicates a potential for drug–drug interactions following co-administration of sacubitril/valsartan and statins [47]. Two studies determining the pharmacokinetic drug–drug interaction potential of sacubitril/valsartan with statins (atorvastatin 80 mg QD and simvastatin 40 mg QD) were conducted in healthy subjects [29, 47]. Multiple-dose administration of sacubitril/valsartan (200 mg BID) with atorvastatin 80 mg QD increased the steady-state C_{max} and AUC of atorvastatin (by 74 and 34%, respectively) and its active metabolites *o*-hydroxyatorvastatin (by 68 and 22%,

respectively) and *p*-hydroxyatorvastatin (by 108 and 26%, respectively) measured on day 5 [29]. Considering the increased C_{max}, caution is recommended when co-administering statins with sacubitril/valsartan.

In contrast to atorvastatin, sacubitril/valsartan (200 mg BID at steady state) showed no marked effects on the pharmacokinetics of simvastatin and its active metabolite, simvastatin acid. Because simvastatin acid was shown to be a more sensitive substrate of OATP1B1 than atorvastatin, it is difficult to explain the observed differences in the impact of sacubitril/valsartan on the pharmacokinetics of atorvastatin and simvastatin acid. However, the magnitude of increase in the AUC of atorvastatin with sacubitrilat/valsartan co-administration was not high, suggesting a limited impact of OATP1B1/1B3 inhibition by sacubitril. This can be attributed to transient inhibition caused by rapid absorption (T_{max} ~ 0.5 h) and elimination (half-life ~ 1.5 h) of sacubitril, leading to a very low plasma concentrations at 4 h post-dose of sacubitril/valsartan. Therefore, the effect is limited to C_{max} of atorvastatin and its metabolites and not to the total exposure. Perhaps this also explains the absence of any marked interaction when sacubitril/valsartan was co-administrated with simvastatin, because both simvastatin and simvastatin acid are absorbed slowly, reaching C_{max} (4 h) after T_{max} of sacubitril.

5.5 Furosemide

Furosemide is a loop diuretic and a known substrate for OAT3, which is involved in furosemide renal excretion [71]. Co-administration with any drug that could potentially inhibit the OAT3 transporter can affect the pharmacokinetics and pharmacodynamics of furosemide. In-vitro studies have shown that sacubitrilat and valsartan can potentially inhibit OAT3 (IC₅₀, 15.2 and 1.1 µM, respectively; data on file for sacubitrilat) [72]. Co-administration of sacubitril/valsartan (at steady state following 5 days administration of 200 mg BID) and furosemide (40 mg) single dose in healthy subjects showed no impact on the steady-state AUCs of sacubitril and sacubitrilat. Valsartan AUC was increased by 15%, which is not clinically significant considering its high variability of exposure (data on file). However, co-administration of both drugs decreased the C_{max} and AUC of furosemide significantly by 50 and 28%, respectively, while urinary excretion of furosemide was reduced by 26%. The potential reduction in the absorption and decrease in the C_{max} of furosemide following sacubitril/valsartan co-administration could be the reason for the observed decrease in AUC. Furosemide absorption and bioavailability are highly variable owing to high inter-subject variability and poor solubility, and further depend on gastric emptying and gastric pH [73]. Furthermore, in previous pharmacokinetic studies, co-

administration of valsartan and furosemide resulted in a 26% reduction in furosemide AUC [74].

Co-administration of sacubitril/valsartan and furosemide compared with the administration of furosemide alone led to a reduction in urine volume within 0–4 h (by 119 mL) and 4–8 h (by 124 mL), while there was no impact on the overall urine volume over 24 h. Furthermore, 24-h natriuresis was decreased by ~30 mmol; this effect was mostly driven by a reduction in natriuresis within the initial 4 h of dosing. However, there was no impact on mean urinary excretion of potassium.

In a post hoc analysis of the pivotal phase III PARADIGM-HF trial, patients receiving furosemide, sacubitril/valsartan ($n = 685$) compared with enalapril ($n = 745$) was associated with a smaller increase in the average daily dose (16.5 vs. 26.2 mg) but with no increase in the median daily dose (0 vs. 20 mg) of furosemide.

In summary, while the exposure of furosemide was decreased with sacubitril/valsartan co-administration, no impact was observed on the pharmacodynamics (24-h urine volume) and the median daily dose of furosemide remained unchanged in the PARADIGM-HF trial.

5.6 Digoxin

Digoxin, a cardiac glycoside, is widely prescribed for the treatment of HFrEF [75, 76]. Digoxin undergoes P-gp-mediated transport in the intestine and kidney [77–79]. Co-administration with a drug that can inhibit/share P-gp transport or elimination can affect the disposition of digoxin, which is relevant owing to its narrow therapeutic index. Sacubitril is a substrate of P-gp.

However, co-administration of sacubitril/valsartan 200 mg BID for 4 days following administration of digoxin for 10 days in healthy subjects did not alter the steady-state pharmacokinetics of digoxin as the GMR and corresponding 90% CIs for both $C_{\max}$ and AUC of the active analytes and digoxin were within 80–125% confidence limits, demonstrating no interaction between sacubitril/valsartan and digoxin [25].

5.7 Nitroglycerin

Nitroglycerin releases nitric oxide that effectively lowers blood pressure (BP) and is indicated for symptomatic treatment of coronary artery disease, a common co-morbidity in patients with HFrEF [80]. Natriuretic peptides, elevated by inhibition of their degradation by sacubitrilat, and nitroglycerin have a common second messenger, cGMP. Therefore, the pharmacodynamic interaction potential between sacubitril/valsartan (200 mg BID) and intravenous nitroglycerin was evaluated in healthy subjects (data on file).

Co-administration with nitroglycerin did not impact the pharmacokinetics of sacubitril/valsartan. The GMR (90%CI) of AUC_{tau} and $C_{\max}$ for sacubitrilat were 1.02 (1.0–1.04) and 0.99 (0.94–1.04), respectively and for valsartan were 1.13 (1.04–1.23) and 1.06 (0.94–1.19), respectively when sacubitril/valsartan administered alone was compared with nitroglycerin co-administration. The pharmacokinetics of nitroglycerin has not been studied considering the technical difficulties of quickly forming nitrate bioanalytics with a short half-life. Therefore, the primary objective was to evaluate a pharmacodynamics interaction.

The dose- and time-dependent reductions in systolic and diastolic BP were not significantly different between administration of nitroglycerin alone and co-administration of nitroglycerin and sacubitril/valsartan. In addition, the maximal BP decrease was similar with nitroglycerin alone (–22.5/–14.4 mmHg) and with the co-administration of nitroglycerin and sacubitril/valsartan (–23.9/–13.3 mmHg). Moreover, the increase in cGMP was not significantly different following co-administration of both drugs compared with sacubitril/valsartan alone, indicating a lack of a pharmacodynamic interaction between sacubitril/valsartan and nitroglycerin. Therefore, the label-recommended dose escalation and clinical monitoring of nitroglycerin is adequate for patients treated with sacubitril/valsartan.

5.8 Sildenafil

Sildenafil, a phosphodiesterase-5 inhibitor, inhibits the degradation of cGMP and is indicated for erectile dysfunction. Considering the high prevalence of erectile dysfunction in patients with HF there is a potential of co-administration with sacubitril/valsartan. Owing to their common second messenger cGMP, the potential for pharmacokinetic and pharmacodynamic interactions was evaluated in patients with mild-to-moderate hypertension (data on file). Co-administration of sildenafil (50 mg) following administration of sacubitril/valsartan (400 mg QD for 5 days) did not impact the $C_{\max}$ and AUC of sildenafil and the AUC of its metabolite, *N*-desmethyl sildenafil. A minor decrease in the $C_{\max}$ of *N*-desmethyl sildenafil (14%) was not considered clinically relevant because it was within the observed pharmacokinetic variability (46%) [81]. Sildenafil did not affect the pharmacokinetics of sacubitrilat; however, it decreased the $C_{\max}$ and AUC of valsartan by approximately 39 and 29%, respectively. Co-administration of sacubitril/valsartan and sildenafil resulted in an additive reduction in ambulatory BP (particularly, daytime and 24-h BP), which may not be desirable in patients with HF. Therefore, sildenafil should be used with caution in patients treated with sacubitril/valsartan.

5.9 Metformin

Metformin is widely prescribed for type 2 diabetes mellitus, a common co-morbidity in HFREF. Following co-administration of sacubitril/valsartan (400 mg QD) and metformin (1000 mg QD) for 4 days, the steady-state pharmacokinetics of all analytes of sacubitril/valsartan remained unaltered, while a decrease in $C_{\max}$ and AUC of metformin by 23% was observed [49]. The clinical relevance of these findings is unknown. However, considering the high inter-individual variability of metformin plasma concentrations and up-titration of metformin dose up to 2250 mg/day based on the glycemic response and tolerability, this decrease is unlikely to be clinically relevant.

5.10 Hydrochlorothiazide (HCTZ)

Diuretics including HCTZ are the first-line treatment for hypertension [82]. A drug–drug interaction study between sacubitril/valsartan and HCTZ was conducted to evaluate the potential for interference with renal clearance as it is the primary elimination pathway for sacubitrilat [22] and HCTZ [83, 84]. Following co-administration of sacubitril/valsartan 400 mg QD and HCTZ 25 mg QD for 4 days in healthy subjects, steady-state $C_{\max}$ of HCTZ was decreased by 26%, whereas an increase in the $C_{\max}$ of sacubitrilat and valsartan by 19 and 16%, respectively, was observed. Although the GMR is 0.85, the 90% CIs of GMRs for AUCs of HCTZ and sacubitrilat were within the 0.80–1.25 interval, whereas the AUC of valsartan was increased by 14% [48]. The observed changes in the AUC of HCTZ and the analytes of sacubitril/valsartan were smaller than the coefficients of variation of estimated pharmacokinetic parameters [48]. Therefore, these observations demonstrated no clinically relevant interactions when sacubitrilat/valsartan and HCTZ were co-administered.

5.11 Amlodipine

Amlodipine, a dihydropyridine calcium channel blocker, is a widely prescribed anti-hypertensive agent [85–88]. Metabolic clearance of amlodipine is primarily mediated by CYP3A4 [89] and is therefore not anticipated to be affected by co-administration of sacubitril/valsartan. Further, co-administration of sacubitril/valsartan (400 mg QD) and amlodipine (10 mg QD) for 5 days in healthy subjects did not impact the steady-state pharmacokinetics of amlodipine or sacubitrilat, while the steady-state $C_{\max}$ and AUC of valsartan increased marginally by 17 and 21%, respectively [48]. These minor changes are not considered to be clinically relevant.

5.12 Oral Contraceptives

Levonorgestrel 150 mg/ethinyl estradiol 30 mg is a widely used combined oral contraceptive (COC) and is primarily metabolized by CYP3A4 [90, 91]. Sacubitril/valsartan analytes did not inhibit/induce CYP3A4 in vitro [22, 36]. As expected, co-administration of COC following administration of sacubitril/valsartan 400 mg QD for 7 days in healthy subjects did not impact the AUC and $C_{\max}$ of ethinyl estradiol and AUC of levonorgestrel, while the $C_{\max}$ of levonorgestrel was decreased by 15% [49]. Because the exposure of levonorgestrel was unchanged and the effect on $C_{\max}$ was small and within the pharmacokinetic variability, the observed changes in $C_{\max}$ are not considered to be clinically relevant and to impact the efficacy of the COC. The pharmacokinetics of sacubitrilat was unchanged, while the $C_{\max}$ and AUC of valsartan were decreased by 16 and 14%, respectively with COC co-administration. These findings suggest no clinically relevant drug–drug interactions between levonorgestrel/ethinyl estradiol and sacubitril/valsartan.

6 Effect of Demographics on Sacubitril/Valsartan Pharmacokinetics

6.1 Body Weight

A pooled analysis from four studies [48, 49] showed no impact of body weight or body mass index on the pharmacokinetics of sacubitrilat and valsartan. Furthermore, a regression analysis showed no statistically significant impact of body weight on steady-state trough plasma concentrations of sacubitrilat and valsartan using pooled data from two studies ($n = 250$) on sacubitrilat/valsartan (100, 200, and 400 mg) [92, 93] conducted in Japanese patients with hypertension (data on file).

6.2 Age and Sex

The effect of age on pharmacokinetics of all the analytes following single-dose administration of sacubitril/valsartan 400 mg was assessed in both young and elderly healthy subjects [94]. In elderly subjects (aged ≥ 65 and ≥ 75 years), the AUC of sacubitrilat was 42% higher compared with young subjects (aged 18–45 years), whereas the $C_{\max}$ was similar (Fig. 3). The AUC and $C_{\max}$ of valsartan were higher by 30 and 24%, respectively, in the elderly subjects compared with young subjects. Decreased clearance, potentially owing to a decrease in renal and hepatic function with age, could be the reason for the observed differences in the pharmacokinetics of sacubitril/valsartan analytes in elderly subjects. However, these

Fig. 3 Effect of demographics and co-morbid disease conditions on the pharmacokinetics of sacubitril/valsartan. *AUC* area under the plasma concentration–time curve, *C_{max}* maximum plasma concentration

are not considered to be clinically relevant as sacubitril/valsartan is shown to be generally safe and well tolerated in patients aged >65 years in the PARADIGM-HF trial [95]. The pharmacokinetics of sacubitrilat and valsartan were similar between male and female subjects (Fig. 3). Hence, no dose adjustment of sacubitril/valsartan is required, regardless of age or sex.

6.3 Race/Ethnicity

A pooled analysis from five studies (Table 2) showed comparable *AUC* and *C_{max}* of sacubitril, sacubitrilat, and valsartan across different races and ethnicities in healthy subjects following the administration of a single dose of 200 mg of sacubitril/valsartan (Fig. 3). The formation of sacubitrilat from sacubitril is mediated by carboxylesterase 1, an enzyme which is shown to have distinct ethnic differences based on genetic polymorphisms and haplotype frequencies [96]. However, these differences did not impact its activity, measured as the ratio of oseltamivir carboxylate/oseltamivir, a carboxylesterase 1-mediated conversion [97]. Our pooled analysis, which revealed no clinically relevant impact of race and ethnicity on pharmacokinetics of sacubitril and sacubitrilat, also suggested that carboxylesterase 1 polymorphisms are unlikely to affect the conversion of sacubitril to sacubitrilat.

7 Pharmacokinetics of Sacubitril/Valsartan in Special Populations

The pharmacokinetics of sacubitril/valsartan was evaluated in patients with renal and hepatic impairment (Fig. 3). The pharmacokinetics of sacubitril/valsartan in the elderly is

described in the previous section. The assessment of safety and efficacy of sacubitril/valsartan in children is currently ongoing; no results are available at the time of compiling this review.

7.1 Patients with Renal Impairment

Renal impairment is a common co-morbidity in patients with HFrEF, with nearly 90% of patients showing some degree of renal dysfunction [41]. Renal excretion is the primary route of elimination of sacubitril (52–68% of the dose), primarily as sacubitrilat, while only ~13% of valsartan and its metabolites are excreted in urine [22]. Renal impairment did not impact the exposure to sacubitril and valsartan; both *C_{max}* and *AUC* of each analyte remained

Fig. 4 Correlation between estimated glomerular filtration rate (eGFR) and systemic clearance of sacubitrilat, an active analyte of sacubitril/valsartan. *CL/F* apparent clearance

unchanged in patients with renal impairment compared with healthy subjects. Compared with healthy subjects, the AUC to sacubitrilat was not impacted by mild (60–89 mL/min/1.73 m²) renal impairment (characterized using the Modification of Diet in Renal Disease formula [98]), whereas it was 2.3-, 2.9-, and 3.3-fold higher in patients with moderate- (30–59 mL/min/1.73 m²) and severe (15–29 mL/min/1.73 m²) renal impairment, and end-stage renal disease (15 mL/min/1.73 m²) without dialysis, respectively (Fig. 3) [44]. No studies have been performed in patients undergoing dialysis. However, sacubitrilat and valsartan are highly bound to plasma protein, and are therefore unlikely to be removed by dialysis. A moderate-to-high correlation between CL/F of sacubitrilat and estimated glomerular filtration rate was observed (R^2 0.6969); the linear relationship between sacubitrilat clearance and estimated glomerular filtration rate could be described by $CL/F = 0.0098 \times eGFR + 0.182$ (Fig. 4). In patients with HFrEF and co-morbid renal impairment, a subgroup analysis of the PARADIGM-HF trial indicated an ~1.8-fold increase in the AUC of sacubitrilat in patients with moderate renal impairment, and an ~2.0-fold increase in those with severe renal impairment, compared with patients with HFrEF and normal renal function. However, no impact on AUC of sacubitril and valsartan was observed (data on file). The starting dose should be adjusted depending on the degree of renal function of patients.

7.2 Patients with Hepatic Impairment

Hepatic clearance is the primary route of elimination of valsartan (~83% of the dose) [37, 99] and contributes to the clearance of sacubitril (37–48% of the dose; primarily as sacubitrilat). Compared with healthy subjects, in patients with mild and moderate hepatic impairment, AUCs increased by 1.5- and 3.4-fold for sacubitril, by 1.5- and 1.9-fold for sacubitrilat, and by 1.2- and 2.1-fold for valsartan, respectively [45]. Despite the increase in the AUC, no impact was observed on the C_{max} of sacubitrilat and valsartan (Fig. 3), while the C_{max} of sacubitril increased by 1.6- and 3.1-fold in patients with mild and moderate hepatic impairment, respectively.

The increase in AUC of sacubitrilat could be attributed to concomitant renal dysfunction observed in a few subjects with hepatic impairment. This was evidenced by the negative correlation of sacubitril AUC and creatinine clearance [45] and is consistent with similar observation in patients with renal impairment [44]. In contrast, the increase in the AUC and C_{max} of sacubitril is not considered to be clinically relevant because sacubitril is an inactive prodrug. The increase in AUC of valsartan was consistent with its primary route of elimination. The

starting dose may need to be adjusted depending on the hepatic function of the patient.

8 Conclusions

Sacubitril/valsartan is a first-in-class angiotensin receptor–neprilysin inhibitor recently approved to reduce the risk of cardiovascular death and HF hospitalization in patients with HFrEF (New York Heart Association II–IV) in several countries worldwide, including USA and Europe. Sacubitril/valsartan is a sodium salt complex of sacubitril (a pro-drug) and valsartan (a well-established angiotensin receptor blocker). Sacubitril undergoes carboxylesterase 1-mediated metabolism to form sacubitrilat, an active neprilysin inhibitor. Pharmacokinetics following single and multiple ascending doses of sacubitril/valsartan revealed rapid absorption of sacubitril and valsartan following oral administration and conversion of sacubitril to sacubitrilat. An increase in AUC was dose proportional for sacubitril and 1.9- and 1.7-fold for sacubitrilat and valsartan, respectively, with a twofold increase in the dose. The bioavailability of valsartan is 60% higher in sacubitril/valsartan than in other marketed tablet formulations. Therefore, a 200-mg dose of sacubitril/valsartan containing 103 mg of valsartan provides systemic exposure similar to that following administration of 160 mg of valsartan in alternate marketed formulations. Sacubitril/valsartan analytes reach steady-state plasma concentrations within 3 days of multiple QD or BID administration. No significant accumulation of either sacubitril or valsartan was observed at the steady state. Accumulation of sacubitrilat was minimal (1.2-fold) with QD administration and significant (1.6-fold) with BID dosing. Food does not have an impact on the pharmacokinetics of sacubitril/valsartan; this was consistent irrespective of dose and formulations. All analytes of sacubitril/valsartan are highly protein bound. The majority of sacubitril (primarily as sacubitrilat) is excreted in urine and a majority of valsartan is excreted in feces.

No clinically relevant drug–drug interactions were observed when sacubitril/valsartan was co-administered with digoxin, warfarin, HCTZ, amlodipine, omeprazole, metformin, carvedilol, or a COC. No pharmacokinetic interaction was observed when sacubitril/valsartan was co-administered with sildenafil; however, caution should be exercised as an additional decrease in BP was observed following co-administration of both drugs. Co-administration of sacubitril/valsartan did not significantly alter the BP-lowering effects of intravenous nitroglycerin. Caution should be exercised when administering sacubitril/valsartan with statins, considering the ~twofold increase in the C_{max} of atorvastatin (with no impact on AUC). However, no significant impact on pharmacokinetics was observed

for simvastatin acid, a sensitive OATP1B1 substrate. While there was a decrease in the exposure of furosemide in the presence of sacubitril/valsartan, no changes in the 24-h urine volume were observed and median daily dose of furosemide was unchanged in the PARADIGM-HF trial. The exposure of metformin was decreased by 23% in the presence of sacubitril/valsartan, however, this is not considered to be clinically significant.

No clinically relevant differences were observed in the pharmacokinetics of sacubitril/valsartan between elderly and young subjects. The pharmacokinetics of sacubitrilat and valsartan were similar among male and female subjects, and across race and ethnicities. In patients with HFrEF, the AUCs of sacubitril, sacubitrilat, and valsartan were higher by 1.6-, 2.1-, and 2.3-fold, respectively, and the peak plasma concentrations of all sacubitril/valsartan analytes were higher by ~1.5-fold. Because the safety and efficacy of sacubitril/valsartan were established in patients with HFrEF in the PARADIGM-HF trial, no dose adjustment is necessary. In patients with renal impairment, AUC of sacubitrilat increased with increasing severity of renal impairment with no impact in patients with mild renal impairment and a 2.3-, 2.9-, and 3.3-fold higher in patients with moderate and severe renal impairment, and end-stage renal disease without dialysis, respectively, compared with healthy subjects. In patients with hepatic impairment, increases in the AUC and C_{max} of sacubitril were not considered clinically relevant because it is an inactive prodrug, while the observed increase in the AUC of valsartan was consistent with its route of elimination. The starting dose may need to be adjusted in patients depending on the renal and hepatic function.

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Compliance with Ethical Standards

Conflict of interest All authors are employees of Novartis except Surya Ayalasomayajula, who was an employee of Novartis during the development of the manuscript and is currently affiliated with Allergan, plc, NJ, USA.

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