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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Unasyn®-S / Sulbactam Sodium, Ampicillin Sodium

PROTOCOL NO.: A9231001

PROTOCOL TITLE: A Multicenter, Unblinded, Non-Comparative Study of Unasyn-S 12 g/Day Evaluating the Safety and Efficacy in Japanese Adult Subjects With Community Acquired Pneumonia

Study Center(s): 22 centers in Japan

Study Initiation and Final Completion Dates: 15 October 2010 to 28 April 2011

Phase of Development: Phase 3

Study Objective(s): The primary objective was to evaluate the clinical efficacy and safety of high-dose sulbactam sodium/ampicillin sodium (SBT/ABPC) for intravenous use (3 g, QID) in patients with moderate to severe community-acquired pneumonia (CAP) for whom injectable antibacterial drugs were indicated and who were judged to require in-hospital treatment.

The secondary objectives were as follows:

To evaluate the bacteriological response of SBT/ABPC.

To measure the plasma concentrations of sulbactam (SBT) and ampicillin (ABPC) following intravenous administration of SBT/ABPC to characterize the pharmacokinetics of SBT/ABPC.

METHODS

Study Design: This is a phase 3, multicenter, unblinded, non-comparative study conducted in Japan. Clinical efficacy was measured at End of Treatment (EOT), at Test of Cure (TOC) which is 7 days after EOT visit, and at Long-Term Follow-Up (LTFU) which is 7 days after TOC visit.

Study schedule is presented in Table 1.

Table 1. Study Schedule

Procedure	Day 1 (before first dose)	Day 1 (after first dose)	Day 4[1)]	EOT[1)] Day of completion (or discontinuation) of treatment	TOC 7 days after completion of treatment	LTFU 7 days after TOC
Visit Window [2)]	Day 0 to 1	–	Day 4 to 5	Day of completion (or discontinuation) of treatment to the following day	5 to 10 days after completion of treatment	7 to 14 days after TOC
Informed Consent	X					
Demographics, Medical History, Underlying Diseases and Complications	X					
Medical Interview and Examination	X		X	X	X	X
Vital Signs	X		X	X	X	X
Body Temperature and Clinical Symptoms	←	—	—	→	X	X
SpO_2	X		X	X	X	XX
Hematology	X		X	X	X	X
Serum Chemistry	X		X	X	X	X
Urinalysis	X		X	X	X	X
Pregnancy Test [3)]	X					X
Chest Radiography (Chest CT if necessary)	X [4)] (Day -1 to 1)		X	X	X	X
Sputum Culture and MIC Testing [5)]	X		X	X	X	X
Sputum Gram Staining [5)]	X		X	X	X	X
Influenza Virus Antigen Test	XX					
Pneumococcal Urinary Antigen Test	X					
PK Sampling [6)]		←	—	→		
Treatment Compliance		←	—	→		
Efficacy Assessment			X	X	X	X
Safety Assessment (Adverse Events)	[7)] ←	—	—	—	—	[8)] →
Concomitant Medications/Therapies	←	—	—	—	—	→
Sample Banking for Exploratory Research [9)]	XX					

X: mandatory, XX: when necessary
EOT=end of treatment, TOC=test of cure, LTFU=long-term follow-up, SpO_2= percutaneous oxygen saturation, CT=computed tomography, MIC=minimum inhibitory concentration, PK=pharmacokinetics
1) Investigators were to determine whether or not to continue treatment on Day 4. When treatment is completed or discontinued before Day 4, EOT procedures on EOT were to be performed instead of those specified on Day 4.
2) In principle, all procedures were to be performed on days designated above.
3) For women of childbearing potential. Pregnancy tests may be re-performed according to institutional review board/independent ethics committee's requests or local regulations.

4) Chest Radiography or CT performed within 48 hours after initiation of study may be used. Radiographies and CTs preformed prior to initiation of study may only be used for patients without apparent improvement, and have no prior antimicrobial therapy, or their prior antimicrobial therapy (administered for more than 3 days) have been confirmed ineffective.
5) Only necessary if sputum is coughed up.
6) Blood samples to be collected at 2 to 3 time points between 0 to 2.5 hours, and at 2 time points between 2.5 to 6 hours after initiation of infusion, on any given treatment during the study.
7) Serious adverse events only.
8) Serious adverse events occurring after LTFU may be collected by telephone or postal mail.
9) To be performed according to protocol (addendum on molecular profiling). Subject consent needed separately from study participation.

Number of Subjects (Planned and Analyzed): The number of subjects planned for this study was 30. A total of 47 subjects were assigned to treatment and were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: The study enrolled moderate to severe CAP patients 16 years or older (younger than 80 years as a general rule) for whom injectable antibacterial drugs were indicated and who were judged to require in-hospital treatment.

Study Treatment: The enrolled subjects received 3 g QID of SBT/ABPC intravenously for 3 to 14 days according to subjects' conditions. SBT/ABPC was intravenously administered over 30 minutes.

Efficacy Endpoints: The primary endpoint was clinical response assessed by the Data Review Committee (DRC) at EOT, TOC, and LTFU.

The secondary endpoints were as follows:

- Clinical response assessed by the investigator (subinvestigator) at EOT, TOC, and LTFU
- Tendency toward clinical improvement assessed by the investigator (subinvestigator) on Day 4
- Bacteriological response assessed by the DRC on Day 4 and at EOT, TOC, and LTFU
- Bacteriological response assessed by the investigator (subinvestigator) on Day 4 and at EOT, TOC, and LTFU

Pharmacokinetic Evaluations: For pharmacokinetic analysis, blood samples were collected at the following time points (at least 4 time points for each subject): 2 to 3 time points between 0 to 2.5 hours after the start of intravenous dosing, 2 time points between 2.5 to 6 hours after the start of intravenous dosing (prior to the start of the next dosing) in any dosing during the period of treatment with SBT/ABPC for intravenous use (Target sampling time points were immediately after the completion of infusion and at 1, 2, 3, and 6 hours after the start of intravenous dosing). Blood samples were assayed for plasma concentrations of SBT and ABPC using a validated liquid chromatography/tandem mass spectrometry.

Safety Evaluations: Adverse events were recorded in the case report form from the time the subject received their first dose of the investigational product to LTFU. Serious adverse events were reported from the time when the subject provided informed consent up to 28 days after the last administration of the investigational product. Clinical laboratory tests were performed, and blood pressure, pulse rate and respiration rate were recorded on Day 1 (prior to dosing) and Day 4; and at EOT, TOC, and LTFU.

Statistical Methods: The Per Protocol Set (PPS) was the primary analysis set for the efficacy analyses. In this study, 2 PPS populations were established: the Clinical Per Protocol Set (CPPS) and the Bacteriologic Per Protocol Set (BPPS). The CPPS consisted of all subjects who received at least 1 dose of the investigational product, had no significant protocol violation, namely regarding inclusion and exclusion criteria, and who underwent

scheduled assessments in the appropriate visit window as specified in the protocol. The BPPS consisted of all subjects in the CPPS, in whom a baseline bacterial pathogen was identified by culture and/or urine antigen test. The Full Analysis Set (FAS) consisted of all subjects who received at least 1 dose of the investigational product.

Regarding the primary analysis of the primary endpoint, the efficacy rate and 95% confidence interval (CI) in the CPPS at TOC were calculated, based on the DRC-assessed clinical response. Regarding the secondary analysis of the clinical response assessed by the DRC, the efficacy rate and 95% CI in the CPPS at EOT and LTFU and the efficacy rate and 95% CI in the BPPS and the FAS on each assessment days (EOT, TOC, and LTFU) were calculated. The frequency and proportion were calculated for the secondary endpoints, and the 95% CIs were also calculated for clinical and bacteriological responses.

In the pharmacokinetic analysis, population pharmacokinetic analysis of SBT/ABPC for intravenous use 12 g/day after intravenous administration was to be performed using the data obtained in the present study. Population pharmacokinetic parameters of SBT and ABPC and those for each subject were to be analyzed with nonlinear mixed-effects modeling. Results of the population pharmacokinetic analysis will be described in the report prepared separately.

Safety was analyzed with all subjects who received at least 1 dose of the investigational product. The safety analysis was performed mainly according to the algorithm and the format specified by Pfizer Data Standards (PDS).

RESULTS

Subject Disposition and Demography: A total of 47 subjects were assigned to treatment in this study, and they all received the investigational product. Table 2 presents a summary of subject disposition and subjects analyzed.

Table 2. Subject Dispositions and Analysis Sets

Number (%) of subjects	
Assigned to treatment	47
Treated	47
Completed	44 (93.6)
Discontinued	3 (6.4)
Lack of efficacy	2 (4.3)
Treatment-related adverse event	1 (2.1)
Analyzed for efficacy	
FAS	47 (100)
CPPS	40 (85.1)
BPPS	28 (59.6)
Analyzed for safety	
Adverse events	47 (100)
Laboratory data	47 (100)

FAS=full analysis set, CPPS=clinical per protocol set, BPPS=bacteriologic per protocol set.

Demographic characteristics for each analysis set are presented in Table 3. None of the parameters showed any major differences among the analysis sets.

Table 3. Demographic Characteristics

	FAS (N=47)	CPPS (N=40)	BPPS (N=28)
Age (years) [n (%)]			
16-44	9 (19.1)	9 (22.5)	6 (21.4)
45-64	11 (23.4)	8 (20.0)	7 (25.0)
65-74	15 (31.9)	12 (30.0)	8 (28.6)
75-79	7 (14.9)	6 (15.0)	4 (14.3)
80<=	5 (10.6)	5 (12.5)	3 (10.7)
Mean±SD	62.3±16.4	61.8±17.5	61.4±17.3
Range	28-85	28-85	28-85
Sex [n (%)]			
Male	26 (55.3)	21 (52.5)	15 (53.6)
Female	21 (44.7)	19 (47.5)	13 (46.4)
Race [n (%)]			
Asian	47 (100)	40 (100)	28 (100)
Weight (kg)			
Mean±SD	52.8±11.8	50.6±10.5	51.9±10.8
Range	31.3-78.7	31.3-78.7	31.3-78.7
Body Mass Index [a] (kg/m^2)			
Mean±SD	20.6±3.7	20.0±3.2	20.4±3.6
Range	13.7-29.0	13.7-29.0	13.7-29.0
Height (cm)			
Mean±SD	159.5±8.6	158.7±8.7	159.3±7.8
Range	137.7-176.7	137.7-176.7	144.3-176.5
Smoking Classification [n (%)]			
Never smoked	18 (38.3)	16 (40.0)	9 (32.1)
Ex-smoker	22 (46.8)	18 (45.0)	15 (53.6)
Smoker	7 (14.9)	6 (15.0)	4 (14.3)

SD=standard deviation, FAS=full analysis set, CPPS=clinical per protocol set, BPPS=bacteriologic per protocol set.
[a] Body Mass Index is calculated as Weight / (Height × 0.01) [2].

Nine different species of causative pathogens were identified from 28 of 40 subjects in the CPPS. A single causative pathogen was identified in 21 subjects and multiple causative pathogens were identified in 7 subjects. The major causative pathogens were *Streptococcus pneumoniae* (14 strains), *Haemophilus influenzae* (9 strains), and *Moraxella catarrhalis* (8 strains).

Efficacy Results: As for the clinical response assessed by the DRC (primary efficacy endpoint), the efficacy rate in the CPPS was 94.6% at TOC (primary analysis), 97.4% at EOT, and 94.4% at LTFU (Table 4).

Table 4. Clinical Response (DRC Assessment, CPPS)

	Total	Clinical response			Efficacy rate[a]	95% CI
		Effective (%)	Ineffective (%)	Indeterminate (%)		
TOC	40	35 (87.5)	2 (5.0)	3 (7.5)	94.6	(81.8, 99.3)
EOT	40	38 (95.0)	1 (2.5)	1 (2.5)	97.4	(86.5, 99.9)
LTFU	40	34 (85.0)	2 (5.0)	4 (10.0)	94.4	(81.3, 99.3)

DRC=data review committee, CPPS=clinical per protocol set, CI=confidence interval, TOC=test of cure, EOT=end of treatment, LTFU=long-term follow-up.
[a] Efficacy rate = effective / (total − indeterminate) × 100.

Major causative pathogens identified at baseline were *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. The DRC-assessed clinical response (efficacy rate) against major causative pathogen in the BPPS across all assessed time points was 91.7% to 100% in subjects with *S. pneumoniae* at baseline, 83.3% to 100% in subjects with *H. influenzae* at baseline, and 87.5% to 100% in subjects with *M. catarrhalis* at baseline. There was no subject whose clinical response was judged to be "ineffective" to any of the causative pathogens at EOT. The clinical response turned out to be "ineffective" to all causative pathogen at TOC or LTFU in the following subjects: 1 subject with *S. pneumoniae* (benzylpenicillin-susceptible: PSSP[a]), 1 subject with *H. influenzae* (β-lactamase-negative ampicillin-susceptible: BLNAS[b]), 1 subject with *M. catarrhalis* (β-lactamase hyperproducing), and 1 subject with *Staphylococcus aureus* (β-lactamase-negative oxacillin-susceptible: MSSA[c]).

The efficacy rate as assessed by the investigator (subinvestigator) was 100% at all of EOT, TOC, and LTFU (Table 5).

Table 5. Clinical Response (Investigator [Subinvestigator] Assessment, CPPS)

	Total	Clinical response			Efficacy rate[a]	95% CI
		Effective (%)	Ineffective (%)	Indeterminate (%)		
TOC	40	38 (95.0)	0	2 (5.0)	100	(90.7, 100)
EOT	40	40 (100)	0	0	100	(91.2, 100)
LTFU	40	34 (85.0)	0	6 (15.0)	100	(89.7, 100)

CPPS=clinical per protocol set, CI=confidence interval, TOC=test of cure, EOT=end of treatment, LTFU=long-term follow-up.
[a] Efficacy rate = effective / (total − indeterminate) × 100.

As for the tendency toward clinical improvement on Day 4 in the CPPS as assessed by the investigator (subinvestigator), it was assessed as present in all 40 subjects (100%) and study treatment was continued (Table 6).

[a] *S.pneumoniae,* Benzylpenicillin ≤ 0.06 μg/mL

[b] *H.influenzae,* Ampicillin ≤1 μg/mL, β-lactamase (−)

[c] *S. aureus,* Oxacillin ≤2 μg/mL

Table 6. Tendency Toward Clinical Improvement at Day 4 (Investigator [Subinvestigator] Assessment)

	Total	Clinical response		
		Effective (%)	Ineffective (%)	Indeterminate (%)
CPPS	40	40 (100)	0	0
BPPS	28	28 (100)	0	0
FAS	47	47 (97.9)	1 (2.1)	0

CPPS=clinical per protocol set, BPPS=bacteriologic per protocol set, FAS=full analysis set

The bacteriological response (eradication rate) by subject in the BPPS was 91.7% to 100% as assessed by the DRC and 95.7% to 100% as assessed by the investigator (subinvestigator) across all assessment time points (Table 7).

Table 7. Bacteriological Response by Subject (DRC Assessment and Investigator [Subinvestigator] Assessment, BPPS)

	N	Bacteriological response						
		Eradication (%)	Presumed eradication (%)	Persistence (%)	Microbial substitution (%)	Indeter-minate (%)	Eradication rate[a] (%)	95% CI
DRC Assessment								
Day 4	27	19 (70.4)	5 (18.5)	0	0	3 (11.1)	100	(85.8, 100)
EOT	28	12 (42.9)	11 (39.3)	1 (3.6)	1 (3.6)	3 (10.7)	96.0	(79.6, 99.9)
TOC	28	6 (21.4)	16 (57.1)	2 (7.1)	0	4 (14.3)	91.7	(73.0, 99.0)
LTFU	28	3 (10.7)	17 (60.7)	1 (3.6)	0	7 (25.0)	95.2	(76.2, 99.9)
Investigator (Subinvestigator) Assessment								
Day 4	27	18 (66.7)	4 (14.8)	1 (3.7)	0	4 (14.8)	95.7	(78.1, 99.9)
EOT	28	13 (46.4)	11 (39.3)	0	0	4 (14.3)	100	(85.8, 100)
TOC	28	5 (17.9)	17 (60.7)	1 (3.6)	0	5 (17.9)	95.7	(78.1, 99.9)
LTFU	28	3 (10.7)	16 (57.1)	0	0	9 (32.1)	100	(82.4, 100)

DRC=data review committee, BPPS=bacteriologic per protocol set, CI=confidence interval, EOT=end of treatment, TOC=test of cure, LTFU=long-term follow-up

[a] Calculated as (total number of subjects assessed as eradication, presumed eradication, and microbial substitution) / (number of assessable subjects excluding subjects in whom bacteriological response was indeterminate) × 100.

The eradication rate by major causative pathogen identified at baseline as assessed by the DRC was 88.9% to 100% for *S. pneumoniae*, 75.0% to 100% for *H. influenzae*, and 87.5% to 100% for *M. catarrhalis* across all assessment time points. Only one strain of *Klebsiella oxytoca* (β-lactamase unknown) was bacteriologically persistent at EOT and the following strains were bacteriologically persistent at TOC or LTFU: 1 strain of *S. pneumoniae* (PSSP), 2 strains of *H. influenzae* (1 β-lactamase-negative ampicillin-resistant [BLNAR[d]] strain and 1

[d] *H.influenzae,* Ampicillin ≥ 4 μg/mL, β-lactamase (−)

BLNAS strain), 1 strain of *M. catarrhalis* (β-lactamase hyperproducing), and 1 strain of *S. aureus* (β-lactamase-negative MSSA).

Clinical signs and symptoms (cough, sputum volumes, nature of sputum, dyspnoea, consciousness disturbed, chest pain, chest rales, and dehydration) in subjects in the CPPS tended to improve from Day 4. Body temperature, white blood cell count, C-reactive protein (CRP), and percutaneous oxygen saturation (SpO_2) also improved from Day 4. The chest x-ray score improved from Day 4, and further improved over the therapeutic course.

Pharmacokinetic Results: The results will be presented in a separate document.

Safety Results: Of the 47 subjects, all-causality adverse events were reported in 30 subjects (63.8%), and treatment-related adverse events were reported in 10 subjects (21.3%). An overview of adverse events is presented in Table 8.

Table 8. Overall Summary of Adverse Events

	All causality	Treatment related
	N=47	N=47
Number of adverse events	71	29
Number (%) of subjects	30 (63.8)	10 (21.3)
Number (%) of subjects with serious adverse events [a]	3 (6.4) [b]	0
Number of subjects with severe adverse events	0	0
Number (%) of subjects with dose or study discontinuation due to adverse events	2 (4.3)	2 (4.3)
Number of subjects with dose reduced or temporary discontinuation due to adverse events	0	0

[a] Data of serious adverse events were based on the safety database.
[b] Includes 1 death.

Treatment-emergent non-serious adverse events reported at an incidence of 3% or more are presented in Table 9.

Table 9. Treatment-Emergent Non-Serous Adverse Events (Incidence ≥ 3%)

	All Causality		Treatment Related	
System Organ Class Preferred Term (MedDRA v14.0)	**N=47**		**N=47**	
Total adverse events (not including serious)	19	(40.4)	7	(14.9)
GASTROINTESTINAL DISORDERS				
Constipation	5	(10.6)	0	
Diarrhoea	3	(6.4)	2	(4.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Pyrexia	2	(4.3)	0	
INFECTIONS AND INFESTATIONS				
Nasopharyngitis	3	(6.4)	0	
INVESTIGATIONS				
Alanine aminotransferase increased	7	(14.9)	5	(10.6)
Aspartate aminotransferase increased	6	(12.8)	5	(10.6)
Blood alkaline phosphatase increased	4	(8.5)	4	(8.5)
Gamma-glutamyltransferase increased	3	(6.4)	3	(6.4)
NERVOUS SYSTEM DISORDERS				
Headache	2	(4.3)	1	(2.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Eczema	2	(4.3)	1	(2.1)
Pruritus	2	(4.3)	1	(2.1)

n (%)

Serious adverse events reported in this study were presented in Table 10. One death was reported 20 days after the end of treatment. An 81-year old woman was reported to have died from drowning, but the investigator considered that it was unrelated to treatment. Two subjects experienced pneumonia (one after the end of study and the other during treatment), but both of these were considered to be unrelated to treatment by the investigator.

Table 10. Serious Adverse Events

	Sex/Age	MedDRA 14.0 Preferred Term	Causality [a]	Action on study drug or procedures	Outcome
1	F/81	Drowning [b]	No	Not applicable [c]	Death
2	M/62	Pneumonia	No	No	Resolved
3	F/67	Pneumonia [b]	No	Not applicable [c]	Resolving

a Causality by investigator.

b Occurred after the end of study.

c Not applicable as the event occurred after the end of the study.

Two subjects (4.3%) discontinued treatment or the study because of adverse events (Table 11). These adverse events were all considered to be treatment-related. One subject with interstitial lung disease (investigator term, interstitial pneumonia aggravated) discontinued both treatment and the study, and 1 subject with aspartate aminotransferase increased discontinued treatment with the investigational product but remained in the study. Resolution of both adverse events was confirmed.

Table 11. Adverse Events Leading to Discontinuation of Treatment

	MedDRA 14.0 Preferred Term	Severity	Outcome	Relation to Study Drug	SAE
1	Aspartate aminotransferase increased [a]	Moderate	Resolved	Suspected	No
2	Interstitial lung disease	Moderate	Resolved	Suspected	No

[a] Discontinued treatment, but did not discontinue the study.

The most common laboratory abnormalities according to the PDS criteria were albumin decreased, blood glucose increased, and monocytes increased. There was no obvious change in blood pressure from baseline. Most of the changes in pulse rate and respiratory rate from baseline were those associated with the recovery from the target disease of the study.

CONCLUSION(S): The following conclusions were derived from the results of the multicenter, unblinded, non-comparative study of high-dose SBT/ABPC for intravenous use (3 g, QID) in moderate to severe CAP patients for whom injectable antibacterial drugs were indicated.

The efficacy rate based on the clinical response assessed by the DRC (primary endpoint) was 94.6% at TOC (primary analysis), 97.4% at EOT, and 94.4% at LTFU.

The bacteriological response (eradication rate) by subject in the BPPS as assessed by the DRC was 91.7% to 100% across all assessment time points. The eradication rate by major causative pathogen as assessed by the DRC was 88.9% to 100% for *S. pneumoniae*, 75.0% to 100% for *H. influenzae*, and 87.5% to 100% for *M. catarrhalis* across all assessment time points.

All reported adverse events were mild to moderate in severity. The adverse events that led to discontinuation of treatment or the study were treatment-related interstitial lung disease (investigator term, interstitial pneumonia aggravated) in 1 subject and treatment-related aspartate aminotransferase increased in 1 subject. Resolution of both adverse events was confirmed. No treatment-related serious adverse events were reported.

The above results demonstrated that the investigational product was well tolerated and posed no safety problem.