European Review for Medical and Pharmacological Sciences 2023; 27: 315-324

Evaluation of the efficacy and safety of NVP-1203 and aceclofenac in patients with acute low back pain and muscle spasm: A randomized, double-blind, active-controlled, parallel, multicenter, phase 3 clinical trial

S. LEE[1], H.-J. KIM[1], J.H. KIM[2], T.K. KIM[3], C.-N. KANG[4], J.-H. LEE[5], J.H. CHO[6], S.H. KIM[7], S.-H. MOON[8]

[1]Department of Orthopedic Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Gyeonggi-do, Republic of Korea
[2]Department of Orthopedic Surgery, Inje University Ilsan Paik Hospital, Gyeonggi-do, Republic of Korea
[3]Department of Orthopedic Surgery, Wonkwang University School of Medicine, Iksan, Republic of Korea
[4]Department of Orthopedic Surgery, Hanyang University Hospital, Seoul, Republic of Korea
[5]Department of Orthopedic Surgery, College of Medicine, Kyung Hee University, Seoul, Republic of Korea
[6]Department of Orthopedic Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[7]Clinical Development, NVP Healthcare Co., Ltd, Suwon, Republic of Korea
[8]Department of Orthopedic Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

Abstract. – OBJECTIVE: Acute low back pain (LBP) is a common condition that can be chronic if not properly treated. Aceclofenac and eperisone hydrochloride are commonly prescribed drugs for acute LBP and muscle spasms. Therefore, NVP-1203, a fixed-dose combination of 100 mg aceclofenac and 75 mg eperisone hydrochloride, is being developed. This study aimed to evaluate the efficacy and safety of NVP-1203 compared to those of a single administration of 100 mg aceclofenac in patients with acute LBP and muscle spasms.

PATIENTS AND METHODS: Overall, 455 patients with acute LBP and muscle spasms were enrolled. The patients were assigned to NVP-1203 or Airtal group (aceclofenac 100 mg). The primary efficacy endpoint was the mean change in the 100 mm pain movement and resting visual analog scale (VAS) scores on treatment day 7.

RESULTS: The mean change in the 100 mm pain movement/resting VAS scores from baseline to day 7 was -49.7 ± 21.5/-41.0 ± 19.4 mm and -38.8 ± 18.9/-33.8 ± 18.0 mm for the NVP-1203 and Airtal groups, respectively. The differences between the two groups were statistically significant (movement, $p < 0.0001$; resting, $p = 0.0002$). Differences in least-square (LS) mean change of the 100 mm pain movement/resting VAS score between the two groups using the analysis of covariance (ANCOVA) model was -10.2/-7.4 mm, and the upper limit of the 95% confidence interval was -6.44/-4.16 mm.

CONCLUSIONS: NVP-1203 is more effective in reducing pain than the 100 mg aceclofenac alone. However, the two drugs have similar safety profiles in patients with acute LBP and muscle spasms.

Key Words:
Eperisone, Aceclofenac, Fixed-dose combination, Muscle relaxant, Acute low back pain, Muscle spasm.

Introduction

Low back pain (LBP) is a neuromuscular disease resulting from occupational characteristics, activities, posture changes, obesity, and pregnancy[1,2]. It is a common condition; > 80% of the general population experiences LBP at least once in their lifetime[3]. Acute LBP recovery is within 4 weeks after onset, but if no recovery occurs within 12 weeks, the recovery decelerates, and the disease tends to become chronic[4]. LBP causes social and economic losses, such as increased medical expenses and decreased productivity; therefore, treatment should be initiated early, depending on the LBP etiology, to prevent progression to chronic pain[5,6].

Corresponding Author: Seong-Hwan Moon, MD; e-mail: shmoon@yuhs.ac

The administration of acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) is recommended as first-line therapy for acute LBP[7]. When the therapeutic effect of a single drug is inadequate, the co-administration of skeletal muscle relaxants with NSAIDs is recommended[4,8,9]. Muscle relaxants are effective when used for a short period in acute LBP. Combined with NSAIDs, muscle relaxants have a synergistic effect compared to that when administered alone[10].

Eperisone hydrochloride is a therapeutic agent that acts between the central nervous system and vascular smooth muscle, relieving skeletal muscle tension, causing vasodilation, and increasing blood flow. Owing to these actions, eperisone effectively controls muscle tension symptoms, such as stiff shoulder, neck pain, headache, and LBP[11]. Several studies[12-14] have demonstrated the efficacy of eperisone in patients with LBP. The side effects of eperisone include nausea, vomiting, and vertigo although the incidence is low[15,16]. Aceclofenac, an NSAID, selectively acts only on cyclooxygenase (COX)-2 and inhibits the conversion of arachidonic acid to prostaglandin, thus, exhibiting anti-inflammatory and analgesic effects. Its selectivity on COX-2 has been demonstrated by an inhibitory concentration (IC50) ratio (COX-2/COX-1) of 0.26, which is between 0.7 and 0.12, the IC50 ratios for celecoxib and rofecoxib, respectively[17]. It is effective against rheumatoid arthritis, ankylosing spondylitis, degenerative arthritis, post-traumatic inflammation, and LBP[17,18]. Moreover, it is well tolerated, and most of its side effects are mild, mainly affecting the gastrointestinal system[19]. The recommended dosage of aceclofenac is 100 mg twice daily[20].

NSAIDs and muscle relaxants are frequently prescribed for LBP treatment. Among these, aceclofenac and eperisone hydrochloride are the most common[20,21]. The co-administration of the two drugs has more advantages, such as increased compliance and efficacy, reduced side effects, and cost, than that of the administration of each drug alone[22]. Nevertheless, there is no drug combining the two components; therefore, NVP-1203, a fixed-dose combination (FDC) drug, containing 100 mg aceclofenac and 75 mg eperisone hydrochloride, is being developed. This study evaluated the efficacy and safety of NVP-1203 compared to those of a single administration of 100 mg aceclofenac in patients with acute LBP and muscle spasms.

Patients and Methods

Study Design

This prospective, multicenter, double-blind, randomized, actively controlled study was conducted at 16 study centers in South Korea from January 2020 to May 2021. It was approved by the institutional review board of each center and registered on ClinicalTrials (NCT04082975; www.clinicaltrials.gov). Informed consent was obtained from all participants. All participants and therapists were blinded to the settings of the study that consisted of a screening visit (visit one), baseline visit (visit two, randomization), day 3 (visit three), and day 7 (visit four, end of study) visits. If participants were receiving analgesics (such as NSAIDs and acetaminophen) or muscle relaxants before the study, a screening test was conducted 24 h after a washout. After the screening test, the participants who met our inclusion criteria were randomized into one of two treatment groups at a 1:1 ratio: the NVP-1203 (test group, FDC of 100 mg aceclofenac and 75 mg eperisone twice daily) or the Airtal group (control group, 100 mg aceclofenac twice daily). Web-based randomization and the randomization program of the Statistical Analysis System (SAS) were employed to achieve a concealed allocation. All the participants were evaluated for efficacy and safety during three visits for seven days and followed up by a telephone communication after the last visit.

Participants

The inclusion criteria were as follows: 1) patients aged ≥19 years who voluntarily agreed to participate; 2) patients diagnosed with spinal muscle spasticity with acute LBP; 3) patients who had pain on a 100 mm pain movement visual analog scale (VAS) score of ≥ 60 mm on visit two (day 1); and 4) 100 mm pain resting VAS score of ≥ 40 mm on visit two. Further, in the inclusion criterion 2), patients diagnosed with spinal muscle spasticity and acute LBP met all of the following criteria: 1) symptoms onset within 4 weeks from visit one; 2) Quebec Task Force Classification 1 (LBP without radiation) or 2 (LBP with radiation not beyond the knee); 3) presence of two or more of the following symptoms: muscle spasm following mild tenderness (including one or more increased pain, body shape changes, and visible muscle spasms), tenderness in the lumbar region (back muscles and spinous process), and worsening pain in the finger-to-floor distance (FFD) test.

Exclusion criteria were as follows: 1) patients with LBP caused by ankylosing spondylitis, spinal fractures, cancers, sciatica, and infection; 2) patients with muscular diseases, such as myositis,

muscular dystrophia, myotonia, and myasthenia; 3) patients with FFD score of ≤ 10 mm; 4) history of an invasive procedure (epidural injection or intramuscular stimulation) for LBP treatment within the previous 8 weeks; 5) history of passive physical therapy (such as oriental medicine treatment, chuna therapy) and iontophoresis within the previous 12 h; 6) history of spine surgery within the previous 24 weeks or scheduled to undergo surgery during the study period; 7) analgesics use (NSAIDs and acetaminophen) within the previous 24 h; 8) opioid use (including tramadol) within the previous three days; 9) muscle relaxants use within the previous 24 h; 10) corticosteroids use orally or by injection within the previous 4 weeks; 11) patients with hypersensitivity to the test drug or any component of the test drug or drug of the same class; and 12) any other severe disease affecting the gastrointestinal or cardiovascular systems, liver, and kidneys.

Protocol violations included errors in prescription/dispensing/drug administration, withdrawal of consent to participate in the trial, violation of inclusion/exclusion criteria, taking prohibited concomitant drugs/therapies during the trial period, violation of the visit schedule, and < 80% or > 120% drug compliance. All protocol violations during the trial period were reported to the institutional review board.

Efficacy and Safety Evaluation

The primary efficacy endpoint was the mean change in the 100 mm pain movement and resting VAS scores on treatment day 7. The secondary efficacy endpoints were the mean change in the 100 mm pain movement and resting VAS scores on day 3 from the baseline, FFD on days 3 and 7 from the baseline, Oswestry Disability Index (ODI) scores on days 3 and 7 from the baseline, and physician's global assessment of response to therapy (PGART) on day 7.

The 100 mm pain VAS was evaluated as pain when moving (pain movement VAS) and at rest (pain resting VAS) at each visit. The score was evaluated when patients bent forward, to the maximum possible extent, in a standing position with both knees extended and both feet attached (pain movement VAS) and when patients sat comfortably (pain resting VAS). The VAS consisted of a 100 mm line with two endpoints representing 'no pain' (0 mm) to 'pain as bad as it could possibly be' (100 mm). The patients were asked to rate their subjective pain level by placing a mark on the line. The evaluation was conducted during visits 1-4.

The patients were asked to bend forward and attempt to reach the floor using their fingertips to evaluate the FFD. Using a ruler, the investigator then measured the distance between the patient's fingers and the floor. The ODI score was used to measure the LBP intensity. The patients were also asked about the treatment effect, and the examination results obtained by physicians were combined. The effectiveness of the medicine was evaluated on the following 5-point Likert scale (PGART): 5 = 'very good' and 1 = 'very poor.'

Adverse events (AEs), clinical laboratory tests, vital signs, physical examination, and electrocardiography were assessed.

Sample Size Calculation

The sample size required to evaluate the superiority of the NVP-1203 over that of the Airtal group was calculated using the following conditions: power of the test, $1 - ß = 0.90$; level of significance, both-sided $\alpha = 0.05$; ratio of sample size, $\lambda = 1$; weighted mean of 100 mm pain VAS score, $\mu t = -57.55$, $\mu c = -49.19$; weighted standard deviation of 100 mm pain VAS score, $\sigma t = 25.65$, $\sigma c = 24.41$[23-26]. The sample size for each group was calculated using the following formula.

The sample size of 189 patients per group was calculated using the above formula. Then, with a dropout rate of 10%, a final sample size of 210 patients per group was obtained.

Statistical Analysis

Data from this study were analyzed in three sets: safety set, full analysis set (FA set), and per protocol set (PP set). The safety set included all patients who received at least one drug during the study and underwent a safety evaluation. The FA set included all patients for whom the primary efficacy endpoints were obtained at least once until the end of the study. Patients who did not evaluate the 100 mm pain movement or resting VAS scores on visits three and four were not included. In the FA set, if a participant was excluded after the trial drug administration and before the end of the trial, or missing data occurred at some point, missing data were replaced by the last observation carried forward (LOCF) method. The PP set included patients who completed the clinical trial without violating the protocol. The data on efficacy evaluation were obtained from both the FA and PP sets; however, the FA set was the main analysis group. The safety evaluation data were obtained from the safety set.

All statistical analyses were performed using the SAS software version 9.4. (SAS Institute, Cary, NC, USA). Continuous variables are expressed as mean, standard deviation, median, minimum, and maximum values, and categorical

variables as numbers and percentages. A two-sided test at a significance level of 5% was performed for all the analyses. In addition, the two-sample *t*-test was used to compare continuous variables between the two groups, and the Chi-square or Fisher's exact test to categorize variables.

Results

Demographic Characteristics

Overall, 455 patients from 16 institutions were enrolled (Figure 1). Except for 34 patients (31 who did not meet the inclusion/exclusion criteria and three who withdrew consent), 421 patients met the inclusion criteria. They were randomly assigned to either the NVP-1203 (210 patients) or the Airtal group (211 patients). Of the 421 patients, 412 completed the clinical trial according to the protocol (NVP-1203 group, 204; Airtal group, 208).

Demographic characteristics are shown in Table I. There were 258 (61.58%) females and 161 (38.42%) males. The age ranges were 19-85 and 19-81 years in the NVP-1203 and Airtal groups, respectively. There were no statistically significant differences between the two groups with respect to sex, age, height, weight, or body mass index. The baseline characteristics of the patients with acute LBP are shown in Table I. The mean duration of acute LBP was 10.09 (±7.01) days in the NVP-1203 group and 10.78 (±7.08) days in the Airtal group. The distribution of acute LBP duration in the NVP-1203 group was '8 days or more' 55.17% (112/203 patients) and 'less than 8 days' 44.83% (91/203 patients) compared to that of the Airtal group; '8 days or more' 55.71% (117/210 patients) and 'less than 8 days' 44.29% (93/210 patients). In the Qubec Task Force Classification, Class 1 (LBP without radiation) was

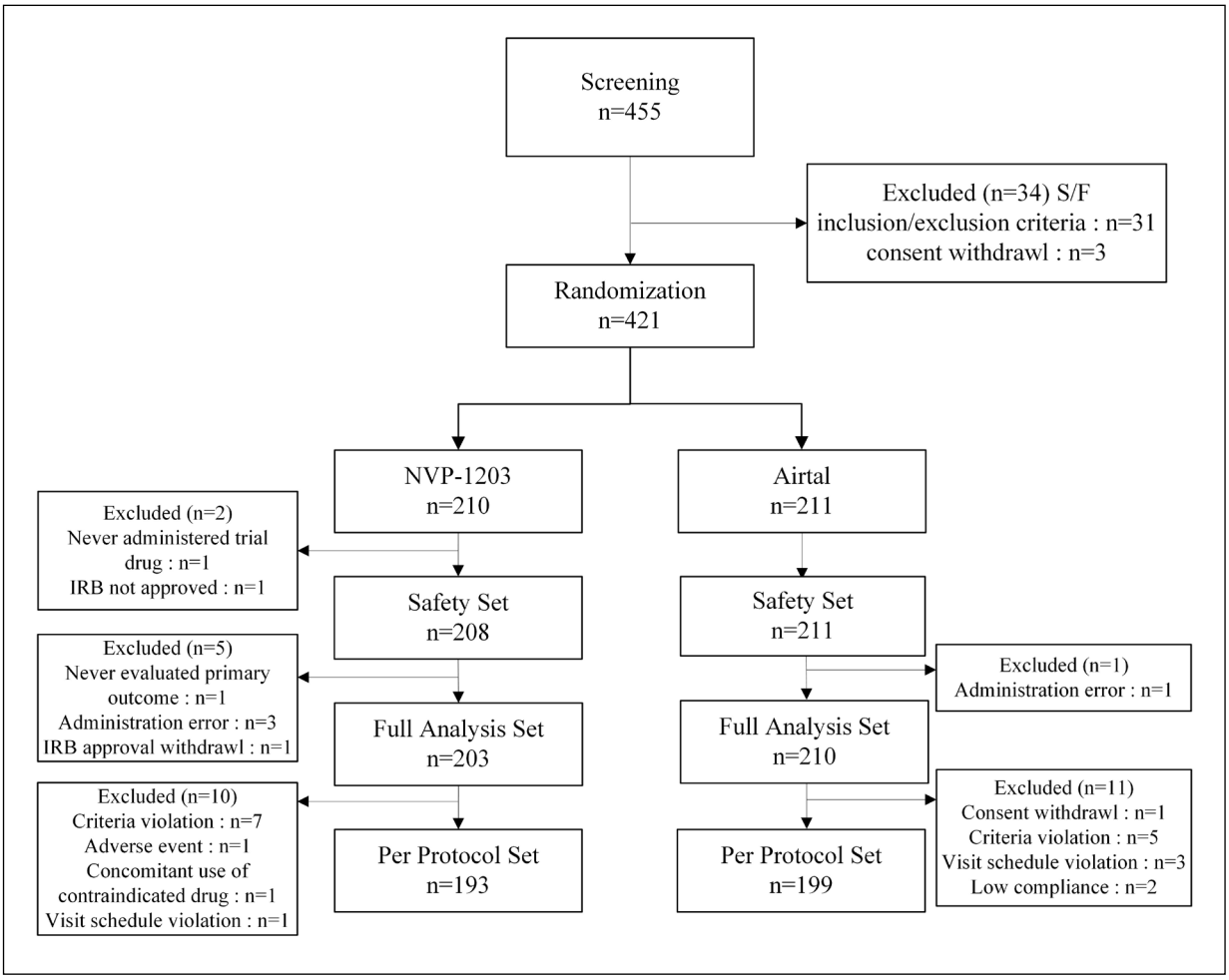

Figure 1. Flowchart of NVP-1203 trial.

Table I. Demographic characteristics (Safety set) and baseline characteristics (FA set)[a].

	NVP-1203 group	Airtal group	*p*-value
Sex	n = 208	n = 211	
Male	84 (40.38%)	77 (36.49%)	0.4129
Female	124 (59.62%)	134 (63.51%)	
Age, Mean±SD[b]	43.26±14.27	44.31±14.29	0.4527
Height, Mean±SD	165.54±9.26	164.48±8.88	0.2346
Weight, Mean±SD	65.40±13.5	65.22±12.60	0.8870
BMI, Mean±SD	23.70±3.41	24.01±3.61	0.3634
Duration	n = 203	n = 210	
Mean±SD	10.09±7.01	10.78±7.08	0.3256
Less than 8 days	91 (44.83%)	93 (44.29%)	
8 days or more	112 (55.17%)	117 (55.71%)	
Quebec Task force Classification			
Class 1c	183 (90.15%)	187 (89.05%)	0.7144
Class 2d	20 (9.85%)	23 (10.95%)	
Muscle spasms when mild tenderness is cause[d]			
Occurrence	156 (76.85%)	144 (68.57%)	0.0593
Not occurrence	47 (23.15%)	66 (31.43%)	
Tenderness in the lumbar region			
Occurrence	187 (92.12%)	198 (94.29%)	0.3811
Not occurrence	16 (7.88%)	12 (5.71%)	
Pain worsening while FFD[e]			
Occurrence	195 (96.06%)	204 (97.14%)	0.5429
Not occurrence	8 (3.94%)	6 (2.86%)	
Compliance, %			
Mean±SD	98.18±6.17	98.17±8.83	0.9879

[a]Full analysis set; [b]Standard deviation; [c]LBP without radiation; [d]LBP with radiation not beyond the knee; [e]Finger-to-floor distance.

90.15% (183/203 patients), and Class 2 (LBP with radiation not beyond the knee) was 9.85% (20/203 patients) in the NVP-1203 group. In comparison, Class 1 was 89.05% (187/210 patients), and Class 2 was 10.95% (23/210 patients) in the Airtal group. The differences between the two groups were not statistically significant concerning all the baseline characteristics of acute LBP.

The overall compliance in the FA set was 98.18 ± 6.17% in the NVP-1203 and 98.17 ± 8.83% in the Airtal group. The two groups had > 98% average compliance in the FA set, and the difference between them was not statistically significant.

Primary Efficacy Results

In the FA set, the mean baseline (visit two) 100 mm pain movement/resting VAS scores were 74.0 ± 10.3/57.3 ± 12.8 mm and 72.9 ± 9.6/57.7 ± 13.0 mm in the NVP-1203 and Airtal groups, respectively. There were no significant differences between the two groups (movement, p = 0.3478; resting, p = 0.8686). However, on day 7, the mean 100 mm pain movement/resting VAS score was 24.3 ± 19.1/16.4 ± 16.3 mm in the NVP-1203 group, which was significantly lower than the mean score of 34.1 ± 19.8/23.9 ± 18.6 mm in the Airtal group ($p < 0.0001$ for movement and resting) (Figure 2, 3). The mean change in the 100 mm pain movement/resting VAS score of the NVP-1203 group from baseline to day 7 was -49.7 ± 21.5/-41.0 ± 19.4 mm *vs.* the -38.8 ± 18.9/-33.8 ± 18.0 mm of the Airtal group, and the differences between the two groups were statistically significant (movement, $p < 0.0001$; resting, $p = 0.0002$). The differences in least-square (LS) mean change of the 100 mm pain movement/resting VAS score between the two groups using the ANCOVA model was -10.2/-7.4 mm, and the upper limit of the 95% confidence interval was -6.44/-4.16 mm, respectively; this means the NVP-1203 was superior to the Airtal group (Table II). Significance was not affected by the Bonferroni correction. Additionally, the results of the PP set were similar to those of the FA set.

Secondary Efficacy Results

In the FA set, there were significant differences in the mean change of the 100 mm pain movement/

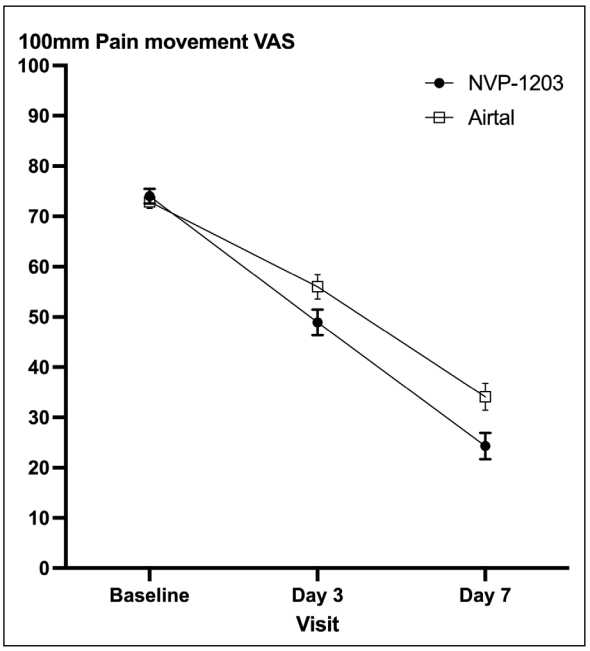

Figure 2. Mean changes with 95% confidence interval in 100 mm pain movement VAS score throughout the study period.

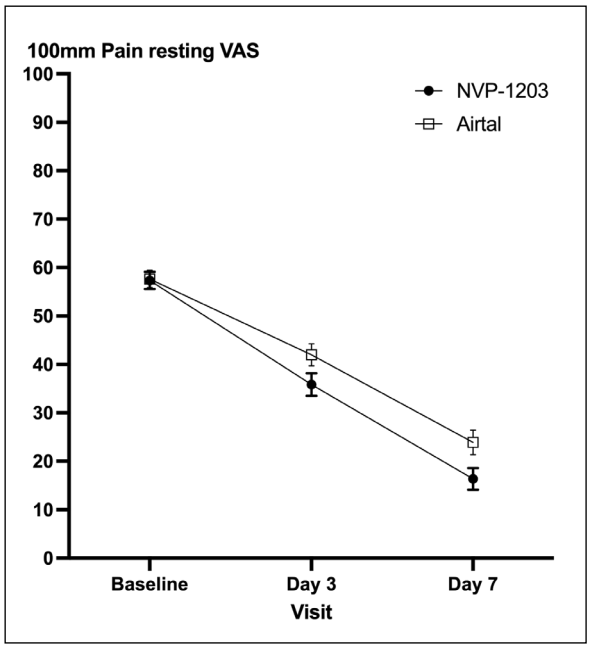

Figure 3. Mean changes with a 95% confidence interval in 100 mm pain resting VAS score throughout the study period.

Table II. Changes in 100 mm Pain movement and resting VAS scores from baseline to days 3 and 7 (FA set)[a].

	NVP-1203 group n = 203	Airtal group n = 210	*p*-value
100 mm Pain movement VAS			
Baseline, Mean±SD	74.03±10.32	72.93±9.57	0.3478
Day 3, Mean±SD	48.91±18.24	56.00±17.66	< 0.0001
Day 7, Mean±SD	24.32±19.05	34.10±19.76	< 0.0001
Difference (Day 3 - Baseline)			
Mean±SD	-25.17±17.37	-16.94±15.47	< 0.0001
LS[b] Mean Change (NVP-1203 - Airtal)	-7.96		< 0.0001
	95% CI (-11.13, -4.79)		
Difference (Day 7 - Baseline)			
Mean±SD	-49.72±21.53	-38.84±18.89	< 0.0001
LS Mean Change (NVP-1203 - Airtal)	-10.15		< 0.0001
	95% CI (-13.86, -6.44)		
100 mm Pain resting VAS			
Baseline, Mean±SD	57.34±12.81	57.65±13.02	0.8686
Day 3, Mean±SD	35.84±16.82	41.99±16.75	0.0026
Day 7, Mean±SD	16.37±16.32	23.90±18.55	< 0.0001
Difference (Day 3 - Baseline)			
Mean±SD	-21.46±15.41	-15.65±14.37	< 0.0001
LS Mean Change (NVP-1203 - Airtal)	-5.92		< 0.0001
	95% CI (-8.71, -3.14)		
Difference (Day 7 - Baseline)			
Mean±SD	-40.98±19.35	-33.75±17.96	0.0002
LS Mean Change (NVP-1203 - Airtal)	-7.42		< 0.0001
	95% CI (-10.67, -4.16)		

[a]Full analysis set; [b]Least-square.

Table III. Secondary efficacy endpoints (FA set)[a].

	NVP-1203 group	Airtal group	*p*-value
Finger-to-Floor Distance			
Baseline, Mean±SD	37.77±15.38	36.99±13.37	0.7356
Day 3, Mean±SD	28.56±13.86	31.10±13.75	0.0809
Day 7, Mean±SD	12.83±10.89	19.44±11.58	< 0.0001
Difference (Day 3 - Baseline)	-9.11±9.27	-6.01±8.24	< 0.0001
Difference (Day 7 - Baseline)	-24.94±17.57	-17.55±12.10	< 0.0001
Oswestry Disability Index			
Baseline, Mean±SD	23.18±9.05	23.08±8.55	0.9208
Day 3, Mean±SD	15.45±7.47	18.22±8.92	0.0031
Day 7, Mean±SD	6.74±5.33	10.50±7.08	< 0.0001
Difference (Day 3 - Baseline)	-7.76±6.74	-4.89±4.89	< 0.0001
Difference (Day 7 - Baseline)	-16.44±9.92	-12.58±7.64	< 0.0001
PGART[b]			
Response[c]	187 (92.12%)	190 (90.48%)	0.5542
No response[d]	16 (7.88%)	20 (9.52%)	

[a]Full analysis set; [b]Physician's global assessment of response to therapy; [c]Response group: response to 'very good' or 'good'; [d]No response group: response to 'no change' or 'poor' or 'very poor'.

resting VAS score from baseline to day 3 (NVP-1203: -25.2 ± 17.4/-21.5 ± 15.4 mm; Airtal: -16.9 ± 15.5/-15.7 ± 14.4 mm) (Table II, Figure 2, 3). The differences in the mean change of the FFD score from baseline to visit three (NVP-1203: -9.1 ± 9.3 cm; Airtal: -6.0 ± 8.2 cm, $p < 0.0001$) and visit four (NVP-1203: -24.9 ± 17.6 cm; Airtal: -17.6 ± 12.1 cm, $p < 0.0001$) between the two groups were statistically significant ($p < 0.0001$ in all the groups) (Table III).

The mean change of the ODI score for the NVP-1203 group from the baseline to day 3/7 was -7.8 ± 6.7/-16.4 ± 9.9 *vs.* -4.9 ± 4.9/-12.6 ± 7.6 for the Airtal group. There were significant differences between the two groups ($p < 0.0001$ for both groups) (Table III).

The PGART was performed at the end of the study period (day 7). If the PGART was 'very good' or 'good,' it was classified as 'response,' and if 'no change' or 'poor,' or 'very poor,' it was classified as 'no response.' The rate of 'response' in the NVP-1203 (92.12%) was higher than that of the Airtal group (90.48%), but there was no significant difference ($p = 0.5542$) (Table III).

Safety results

In the safety set, there were no differences in the total study period between the two groups (14.87 ± 1.35 days in the NVP-1203 and 14.89 ± 1.36 days in the Airtal group, $p = 0.8468$). Adverse effects (AE) were reported in 19 (9.13%) and 13 (6.16%) patients in the NVP-1203 and Airtal groups, respectively. Adverse drug reactions (ADRs) were also reported in seven (3.37%) and six (2.84%) patients in the NVP-1203 and Airtal groups, respectively. There was only one serious AE (suicide attempt) in the NVP-1203 and none in the Airtal group (Table IV).

Discussion

This randomized, double-blind, multicenter, phase III clinical trial compared the efficacy and

Table IV. Safety evaluation (Safety set).

n = 208	NVP-1203 group n = 211	Airtal group	*p*-value
Administration period	14.87±1.35	14.89±1.36	0.8468
Adverse events	19 (9.13%)	13 (6.16%)	0.2519
Serious AEs[a]	1 (0.48%)	0 (0.00%)	0.4964
Adverse drug reactions	7 (3.37%)	6 (2.84%)	0.7581
Serious ADRs[b]	0 (0.00%)	0 (0.00%)	NA

[a]Adverse events; [b]Adverse drug reactions.

safety of NVP-1203 (FDC drug containing 100 mg aceclofenac and 75 mg eperisone) with Airtal (aceclofenac, 100 mg) alone in patients with acute LBP and muscle spasm. By analyzing the primary efficacy endpoint in the FA set as the main analysis set, the difference in LS mean change in the 100 mm pain movement and resting VAS from baseline to day 7 between the two groups was -10.15 mm and -7.42 mm, respectively. In addition, the 95% bilateral confidence interval limit was -6.44 and -4.16 implying a superior pain reduction effect of NVP-1203 than Airtal. Similarly, in the analysis of FFD and ODI, NVP-1203 showed a significantly greater improvement than that of Airtal. Therefore, NVP-1203 therapy is superior to aceclofenac monotherapy for pain reduction and functional improvement in acute LBP.

Several studies[10,27,28] have evaluated the concomitant use of NSAIDs and muscle relaxants. Patel et al[10] demonstrated that combining chlorzoxazone, a muscle relaxant, and ibuprofen resulted in superior pain VAS reduction compared to that with ibuprofen monotherapy in acute LBP. In that open-label study[27], a 78.2% reduction in the VAS score with the combination therapy was noted on day 7. In another open-label study[28] conducted on 100 patients with acute LBP and muscle spasms, combination therapy with eperisone and ibuprofen was more effective than ibuprofen monotherapy. A significant pain reduction, > 50% of the baseline, was more in the combination therapy group compared to that in the monotherapy group (72.4 *vs.* 46.7%, $p < 0.05$). Similar to the results of these previous studies[10,27,28] our study showed that the concomitant use of aceclofenac and eperisone exerted superior efficacy to that of aceclofenac monotherapy. It was thought that since eperisone worked as a muscle relaxant, concomitant use of aceclofenac and eperisone had superior FFD improvement causing superior pain reduction.

As described earlier, NVP-1203 has several advantages over administering 100 mg aceclofenac and 75 mg eperisone separately. First, the FDC simplifies the number of medications and schedules. The pill burden is reduced since patients only need to take one tablet, and the compliance and adherence to therapy are higher than those with taking two tablets[29]. Second, FDC has socio-economic benefits because its production saves more resources than that when making each drug separately. Third, the FDC allows physicians to systematically apply the best treatment without rambling with different options and doses.

The safety analysis showed that NVP-1203 and aceclofenac monotherapy were safe for treating acute LBP with muscle spasms. Of the 419 patients, AE occurred in 19 (9.13%, 35 cases) patients in the NVP-1203 and 13 (6.16%, 16 cases) patients in the Airtal group. The differences in the incidence of AEs and ADRs between the two groups were not statistically significant ($p = 0.2519$ and 0.7581, respectively). The most frequent ADR in the NVP-1203 group was 'dyspepsia'; 'drowsiness' and 'nausea' were observed in the Airtal group, but none of the AEs was serious except one. The serious AE in one patient (0.48%) in the NVP-1203 group was a 'suicidal attempt'; we determined this was not drug-related, but rather due to substance abuse (alcohol overdose).

This study has several limitations. First, acute LBP can persist up to 4 weeks; if it lasts longer, it can transit to subacute or chronic LBP[4]. However, in this trial, only 1 week of short-term follow-up was performed; hence additional studies would be needed in case of long-term NVP-1203 use. Second, acute LBP might be a self-limiting condition in many cases[6,30]; however, this trial did not include a placebo control group. Third, this trial did not compare NVP-1203 with placebo because NVP-1203 had a superior pain reduction effect than that of the placebo in the phase 2 trial of NVP-1203 (NCT03341832; www.clinicaltrials.gov). In the phase II trial, the difference in LS mean changes in the 100 mm pain movement and resting VAS from baseline to day 7 between the test drug (n = 31) and placebo group (n = 30) were -26.67 mm and -30.20 mm, respectively implying superior pain reduction effect of the NVP-1203 than that of the placebo. Therefore, we confirmed the efficacy of the given drug. NVP-1203 is a simple mixture of 100 mg aceclofenac and 75 mg eperisone and is one of the most commonly prescribed drugs; however, whether this combination is the most appropriate one, has not been investigated.

Conclusions

NVP-1203, an FDC of 100 mg aceclofenac and 75 mg eperisone, is more effective in reducing pain than that by 100 mg aceclofenac alone. Nevertheless, the two drugs have similar safety profiles in patients with acute LBP and muscle spasms.

Conflict of Interests

SH Kim is an NVP Healthcare Co., Ltd employee. The other authors declare no conflict of interest.

Authors' Contributions
SH Lee and HJ Kim contributed equally to this work. Conceptualization, SH Moon; formal analysis, HJ Kim, SH Moon; resources, HJ Kim, JH Kim, TK Kim, CN Kang, JH Lee, JH Cho, and SH Moon; data curation; SH Kim; writing draft, SH Lee and HJ Kim; supervision, SH Moon. All authors have read and agreed to the published version of the manuscript.

Acknowledgments
The authors thank Kyu-Jung Cho, Young Do Koh, Hyoung Yeon Seo, Jae Hyup Lee, Moon Soo Park, Young-Hoon Kim, Si-Young Park, Jae Ho Yang, and Ji-Won Kwon for this clinical trial.

Funding
This study was supported by a research fund from NVP Healthcare Co., Ltd.

Ethics Approval
This study was approved by the institutional review board of each center and registered on ClinicalTrials (NCT04082975; www.clinicaltrials.gov).

Informed Consent
Informed consent was obtained from all the participants.

Data Availability Statement
Data can be obtained from the corresponding author upon reasonable request.

ORCID ID
Seong-Hwan Moon: 0000-0002-5165-1159

References

1) Vrbanic TS. [Low back pain--from definition to diagnosis]. Reumatizam 2011; 58: 105-107.
2) Ehrlich GE. Low back pain. Bull World Health Organ 2003; 81: 671-676.
3) Grabiner MD, Jeziorowski JJ, Divekar AD. Isokinetic measurements of trunk extension and flexion performance collected with the biodex clinical data station. J Orthop Sports Phys Ther 1990; 11: 590-598.
4) Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of P, Denberg TD, Barry MJ, Boyd C, Chow RD, Fitterman N, Harris RP, Humphrey LL, Vijan S. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2017; 166: 514-530.
5) Katz JN. Lumbar disc disorders and low-back pain: socio-economic factors and consequences. J Bone Joint Surg Am 2006; 88 Suppl 2: 21-24.
6) Pengel LHM. Acute low back pain: systematic review of its prognosis. BMJ 2003; 327: 323-320.
7) Hong J-Y, Song K-S, Cho JH, Lee JH, Kim NH. An Updated Overview of Low Back Pain Management. Asian Spine J 2021; doi: 10.31616/asj.2021.0371.
8) Casazza BA. Diagnosis and treatment of acute low back pain. Am Fam Physician 2012; 85: 343-350.
9) Witenko C, Moorman-Li R, Motycka C, Duane K, Hincapie-Castillo J, Leonard P, Valaer C. Considerations for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. P T 2014; 39: 427-435.
10) Patel HD, Uppin RB, Naidu AR, Rao YR, Khandarkar S, Garg A. Efficacy and Safety of Combination of NSAIDs and Muscle Relaxants in the Management of Acute Low Back Pain. Pain Ther 2019; 8: 121-132.
11) Ryu JH, Kim JI, Kim HS, Noh GJ, Lee KT, Chung EK. Pharmacokinetic Interactions Between Pelubiprofen and Eperisone Hydrochloride: A Randomized, Open-label, Crossover Study of Healthy Korean Men. Clin Ther 2017; 39: 138-149.
12) Cabitza P, Randelli P. Efficacy and safety of eperisone in patients with low back pain: a double blind randomized study. Eur Rev Med Pharmacol Sci 2008; 12: 229-235.
13) Sakai Y, Matsuyama Y, Nakamura H, Katayama Y, Imagama S, Ito Z, Okamoto A, Ishiguro N. The effect of muscle relaxant on the paraspinal muscle blood flow: a randomized controlled trial in patients with chronic low back pain. Spine (Phila Pa 1976) 2008; 33: 581-587.
14) Chandanwale AS, Chopra A, Goregaonkar A, Medhi B, Shah V, Gaikwad S, Langade DG, Maroli S, Mehta SC, Naikwadi A, Pawar DR. Evaluation of eperisone hydrochloride in the treatment of acute musculoskeletal spasm associated with low back pain: a randomized, double-blind, placebo-controlled trial. J Postgrad Med 2011; 57: 278-285.
15) Sartini S, Guerra L. Open experience with a new myorelaxant agent for low back pain. Adv Ther 2008; 25: 1010-1018.
16) Bavage S, Durg S, Ali Kareem S, Dhadde SB. Clinical efficacy and safety of eperisone for low back pain: A systematic literature review. Pharmacol Rep 2016; 68: 903-912.
17) Dooley M, Spencer CM, Dunn CJ. Aceclofenac. Drugs 2001; 61: 1351-1378.
18) Moore RA, Derry S, McQuay HJ. Single dose oral aceclofenac for postoperative pain in adults. Cochrane Database Syst Rev 2009; 2009: CD007588.
19) Legrand E. Aceclofenac in the management of inflammatory pain. Expert Opin Pharmacother 2004; 5: 1347-1357.

20) Park MG, Yoo JD, Lee KH. Current Guidelines for Non-Steroidal Anti-Inflammatory Drugs. J Korean Orthop Assoc 2020; 55: 9-28.

21) Park G, Sohn JE, Moon M, Lee JY, Kang HR, Kang DY. Characteristics of Adverse Drug Reactions of Central Muscle Relaxants Including Eperisone: Analysis of KAERS Data. Journal of Pharmacoepidemiology and Risk Management 2020; 12: 79-84.

22) Shenfield GM. Fixed combination drug therapy. Drugs 1982; 23: 462-480.

23) Kumar S, Rani S, Siwach R, Verma P. To compare the efficacy and safety of fixed dose combination of thiocolchicoside and aceclofenac versus chlorzoxazone, aceclofenac and paracetamol in patients with acute lower backache associated with muscle spasm. Int J Appl Basic Med Res 2014; 4: 101-105.

24) Pareek A, Chandurkar N, Chandanwale AS, Ambade R, Gupta A, Bartakke G. Aceclofenac-tizanidine in the treatment of acute low back pain: a double-blind, double-dummy, randomized, multicentric, comparative study against aceclofenac alone. Eur Spine J 2009; 18: 1836-1842.

25) Schattenkirchner M, Milachowski KA. A double-blind, multicentre, randomised clinical trial comparing the efficacy and tolerability of aceclofenac with diclofenac resinate in patients with acute low back pain. Clin Rheumatol 2003; 22: 127-135.

26) Berry H, Hutchinson DR. Tizanidine and ibuprofen in acute low-back pain: results of a double-blind multicentre study in general practice. J Int Med Res 1988; 16: 83-91.

27) Chou R, Huffman LH, American Pain S, American College of P. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med 2007; 147: 505-514.

28) Pinzon RT, Wijaya VO, Paramitha D, Bagaskara RR. Effects of Eperisone Hydrochloride and Non-Steroid Anti-Inflammatory Drugs (NSAIDs) for Acute Non-Specific Back Pain with Muscle Spasm: A Prospective, Open-Label Study . Drug Healthc Patient Saf 2020; 12: 221-228.

29) Pourkavoos N. Unique Risks, Benefits, and Challenges of Developing Drug-Drug Combination Products in a Pharmaceutical Industrial Setting. Comb Prod Ther 2012; 2: doi.org/10.1007/s13556-012-0002-2.

30) Dwyer AP. Backache and its prevention. Clin Orthop Relat Res 1987; (222): 35-43.