CLINICAL TRIAL SUMMARY REPORT

A PHASE III, MULTICENTER, RANDOMIZED, PARALLEL GROUPS STUDY TO ASSESS THE EFFICACY AND SAFETY OF 0,5 MG TIZASPRAY® ADMINISTERED INTRANASALLY VERSUS SIRDALUD® 2 MG TABLETS, IN PATIENTS WITH ACUTE LOW BACK PAIN

Administrative information	**Protocol number:** TZSA2 **EudraCT number:** 2014-003040-12 **Date of trial report:** September 20th, 2017 Is the trial part of a Paediatric Investigation Plan? YES☐ NO ☒
Trial design	The study was a phase III, randomized, controlled, multicenter study with two parallel groups of patients. The study was aimed to evaluate the efficacy and safety of 0,5 mg Tizaspray® administered intranasally versus Sirdalud® 2 mg administered orally, in patients suffering from acute low back pain.
Background for conducting the trial	Tizanidine HCl is the active substance of the medicinal product Sirdalud® tablets 2 mg, 4 mg, and 6 mg. Tizanidine HCl is a centrally acting skeletal muscle relaxant: it is a α_2-adrenergic agonist structurally related to clonidine and acts mainly at spinal and supraspinal level to inhibit excitatory interneurones. It is used for the symptomatic relief of spasticity associated with multiple sclerosis or with spinal cord injury or disease. It is also used in the symptomatic treatment of painful muscle spasm associated with musculoskeletal conditions. The compound has marketing approval in UK, USA, Canada, Italy, Japan, Belgium, Brazil, Denmark, Egypt, Finland, Germany, and Austria. MDM, the Sponsor of this study, has developed a new patented pharmaceutical form, nasal spray solution, that allows the administration through the nasal route of a therapeutic dose, avoiding the metabolic hepatic first-pass effect, increasing the rate of absorption, and likely reducing the side effects. Two phamacokinetics studies on twelve healthy volunteers showed that the nasal route produces larger absorption and higher plasma concentrations of the drug than the oral route. The overall results of the PK studies suggested that 1 mg as Tizanidine base by intranasal administration produces plasma levels similar to those of tablets containing 4 mg as Tizanidine base. The first PK investigation carried out on healthy volunteers showed that Tizaspray® was well tolerated after IN administration of 2 or 4 mg, excepting for transient nasal mucosa burning due to the formulation. The drug resulted to be better and more rapidly absorbed after IN administration than after oral administration, as proved by t_{max}, C_{max} and AUC_{0-t} values. The second PK study with a lower dose (1 mg as base) proved that the IN dose produces plasma levels close to those obtained after the therapeutic oral dose, 4 mg. Tizaspray® 0.5 mg and Tizaspray® 1 mg were tested in a phase II study in 72 patients suffering from acute low back pain, versus the reference drug Sirdalud® (tizanidine HCL 4 mg tablet). The efficacy and safety were assessed based on primary objectives (pain intensity and pain relief), secondary objectives (double stopwatch method, “hand-to-floor” distance, use of rescue medication) and systemic and local tolerability over 7 days of treatment t.i.d. The results showed the non-inferiority of Tizaspray® 0.5 mg vs Sirdalud® tablets 4 mg and therefore Tizaspray® 0.5 mg was proposed for this phase III clinical trial. This phase III study was aimed to evaluate the efficacy and safety of Tizaspray® 0.5 mg compared to Sirdalud® 2 mg (that is the dosage most commonly used in clinical practice) for the treatment of acute low back pain.

Participants of the trial	**Eligibility criteria for participants** **Diagnosis and main criteria for inclusion:** *Inclusion Criteria* 1. Age between 18 and 65 years old 2. Average low back pain intensity moderate to severe (≥ 60 mm in the VAS) at Visit 1 3. Positivity to Schober's test (i.e. measure < 5 cm) at Visit 1 4. Acute low back pain started at least 24 hours prior to inclusion in the trial and more than 6 weeks after the last episode of acute low back pain 5. Negative pregnancy test for women of childbearing potential (to be performed at Visit 1) and use of an acceptable mean of contraception (condom or mechanical methods) in the previous 2 months and for whole duration of the study 6. Signed Informed Consent *Exclusion Criteria* 1. History of chronic low back pain 2. Current treatment with drugs having significant effects at the alpha2 receptors whether agonist (i.e., clonidine, methyldopa) or antagonist (i.e., phenothiazines, imipramine) 3. Current treatment with any other muscle relaxant or any drugs having muscle relaxant properties 4. Known allergies, hypersensitivity, or intolerance to tizanidine or paracetamol or any excipients used in their manufacture (included patients with known rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption) 5. Signs of nasal congestion, nasal polyps, mucosal lesions of the nostrils, postnasal drip of any etiology or any clinically significant nasal pathology that may affect the absorption of study medication or the assessment of safety 6. Evidence of clinically unstable disease, as determined by medical history, physical examination, that, in the Investigator's opinion, preclude entry into the study 7. Spinal surgery within 1 year of study entry 8. Evidence of clinical gastrointestinal malabsorption 9. Use of steroids within 3 months of study entry or any other long-term treatment with steroids 10. Use of NSAID's or other anti-inflammatory drugs 6 hours prior to study inclusion 11. Use of fluvoxamine or ciprofloxacin, or other inhibitors of CYP1A2 such as antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, fluoroquinolones (enoxacin, pefloxacin, norfloxacin), rofecoxib, oral contraceptives, and ticlopidine 12. Use of hypnotics or other CNS depressants 13. Blood pressure <100/70 mmHg 14. History of lumbar spinal stenosis, fibromyalgia, or ankylosing spondylitis 15. Severe scoliosis 16. More severe pain in a region other than the lower back 17. Acute low back pain associated with chills or fever 18. Pregnancy, breast feeding 19. Treatment with another investigational agent within the last 30 days 20. Known or suspected history of alcohol or drug abuse based on medical history, physical examination, or the Investigator's clinical judgment **Settings and locations where the data were collected** The study was conducted at 5 clinical sites in Italy and 5 clinical sites in Romania. *Site no. 1 – coordinating site*

	Prof. Paolo Cabitza (Study Coordinator) Prof. Pietro Randelli / Dr. Paolo Arrigoni (Principal Investigator) Ortopedia e Traumatologia II I.R.C.C.S. Policlinico San Donato Via R. Morandi, 30 - S. DONATO M.SE - MILANO *Site no. 2* Dr. Fabio Lazzaro Ortopedia Traumatologia Oncologica A.O. Istituto Ortopedico “Gaetano Pini” P.zza A. Ferrari, 1 - MILANO *Site no. 3* Prof. Giuseppe Sessa Clinica Ortopedica Azienda Ospedaliero-Universitaria "Policlinico Vittorio-Emanuele" Via S. Sofia,78 – CATANIA *Site no. 4* Prof. Fabio Catani SC Ortopedia e Traumatologia Azienda Ospedaliero Universitaria Policlinico di Modena Via del Pozzo, 71 - MODENA *Site no. 5* Prof. Giovanni Restuccia U.O.C. Ortopedia e Traumatologia A.O. di Rilievo Nazionale e di Alta Specializzazione Garibaldi Piazza Santa Maria di Gesù, 5 - CATANIA ***ROMANIA*** *Site no. 1 – coordinating site* Dr. Delia Cinteza Institutul National de Recuperare, medicina Fizica si Balneoclimatologie - Clinica Recuperare Neurologica IV - Blvd Ion Mihalache, nr 11A, Sector 1 - BUCURESTI *Site no. 2* Dr. Augustin Dima Institutul National de Recuperare, medicina Fizica si Balneoclimatologie - Clinica I - Str Sf. Dumitru, nr 2 - BUCURESTI *Site no. 3* Dr. Mihaela Cristina China Medical Center for Diagnosis and Treatment Dr. Ovidiu Cristian Chiriac. 120 Cuza Voda Street, District 4. BUCURESTI *Site no. 4* Dr. Bogdan Corneliu Andor S.C. Medicali’s SRL, Departament Ortopedie si Traumatologie Str. Iancu Flondor, nr 47 - TIMISOARA *Site no. 5* Dr. Doina Rosu S.C. Medicala Gados, Departament Medicina Interna Str. Cozia, nr 10 - TIMISOARA

Interventions	A total number of 236 subjects were enrolled and analysed: Patients were randomized to receive one of the two treatments according to a 1:1 randomization scheme via an electronic Case Report Form (eCRF) based randomization system. Patients attended 3 Visits: Visit 1 on Day 1 (screening and randomization), Visit 2 on Day 3 (follow-up visit) and Visit 3 on Day 8 (end of study/end of treatment).
Objective(s) of the Trial	**Primary** 1. To evaluate the muscle relaxant activity of Tizaspray® 0.5 mg compared to Sirdalud® (tizanidine 2 mg) as assessed by the "hand-to-floor" distance at baseline, day 3 and day 8. 2. To evaluate the efficacy of Tizaspray® 0.5 mg for the treatment of acute low back pain compared to Sirdalud® 2 mg, as assessed by the Low Back Pain Intensity Scale (0 to 100 mm VAS) over maximum 7 days of treatment. 3. To evaluate the muscle relaxant activity of Tizaspray® 0.5 mg compared to Sirdalud® 2 mg tablets as assessed by the Schober's test (positive/negative) at baseline, day 3 and day 8. **Secondary** 1. To evaluate the efficacy of Tizaspray® 0.5 mg for the treatment of acute low back pain compared to Sirdalud® 2 mg, as assessed by the Patient's Pain Relief Evaluation on days 3 and 8. 2. To determine the efficacy of Tizaspray® 0.5 mg compared to Sirdalud® 2 mg 30, 60, 90 and 180 minutes after the second administration (day 1, 2 and 3) as assessed by the Low Back Intensity Scale (0 to 100 mm VAS). 3. To evaluate the efficacy of Tizaspray® 0.5 mg for the treatment of acute low back pain compared to Sirdalud® 2 mg, as measured by the Roland Disability Questionnaire (RDQ) on days 3 and 8. 4. To evaluate the muscle relaxant activity of Tizaspray® 0.5 mg compared to Sirdalud® 2 mg tablets as assessed by the Schober's test difference in cm between day 1 and day 3 and between day 1 and day 8. 5. To evaluate the use of "rescue medication" (paracetamol) for low back pain. **Safety** To investigate the overall safety and tolerability of Tizaspray® 0.5 mg administered t.i.d.

Outcome measures	Primary Efficacy The primary efficacy endpoints included "Hand-to-floor" distance, pain intensity and Schober's test. • "Hand-to-floor" distance was evaluated by the Investigators who asked the patients to bend forward and try to touch the floor with the fingers; the remaining distance between fingers and ground ("hands-to-floor") was measured by means of a ruler (mm).The changes in "Hand-to-floor" distance between day 1 and day 3 and between day 1 and day 8 were assessed. • Pain intensity on movement, at rest and while sleeping was assessed at days 1 to 7 on a VAS ranging from 0 ("no pain") to 100 mm ("worst pain").The improvement in pain intensity for each patient was estimated through the difference in VAS score between baseline (day 1) and each time point (days 2, 3, 4, 5, 6, 7), separately for movement, rest and sleep. The differences between baseline and each visit was also assessed. • Schober's test assessed the amount of lumbar flexion. In this test, a first mark was made on the back in the midpoint on the imaginary line joining the posterior superior iliac spines, on the vertebral column. The examiner then placed a mark 5 cm below the first mark and another mark 10 cm above the first mark. The patient was then instructed to touch his toes. If the increase in distance between the two marks on the patients spine is less than 5 cm then this is indicative of a limitation of lumbar flexion (Schober's test positive).Schober's test was performed at baseline, day 3 and day 8. At baseline, all patients should be positive to the test (i.e. measure < 5 cm). At day 3 and day 8 the proportion of patients with negative test (i.e. measure ≥ 5 cm) was assessed. Secondary efficacy assessments • Patient's Pain Relief Evaluation on days 3 and 8 with respect to baseline was reported by the patient on a 5-point Likert Scale (0-No pain relief to 4-Total pain relief) • The intensity of pain 30, 60, 90 and 180 minutes after the second administration on days 1, 2 and 3 was reported by the patients by a VAS. • At visits the patients were requested to complete the Roland Disability Questionnaire (RDQ), which measures 24 activity limitations due to low back pain (score 0–24: higher score, increased disability). • The changes in Schober's test measure in cm between baseline and days 3 and 8 were also assessed • The number of Rescue Medication (Paracetamol) tablets used was assessed. Safety assessment Adverse events and vital signs were assessed during the study.
Randomisation implementation	The randomization list was generated by Latis, using the module RALLOC of STATA/IC 13.1 for Windows (StataCorp LP, College Station, TX, USA). The randomization list was split in blocks of four treatment kits each in order to avoid any major displacement at any time both within and between clinical sites. Each block included two kits for each treatment group in a randomized order. Once eligibility was established according to Inclusion/Exclusion Criteria, the Investigator randomized electronically the patient and assigned the kit number as indicated by the eCRF system. The assigned kit number was automatically recorded by the eCRF. Study medication was delivered to clinical sites according to a randomization scheme 1:1 and to the randomization list. Each clinical site was re-supplied when the study medication was almost totally allocated to enrolled patients

Blinding	The study was open label
Statistical methods	*Primary endpoints* The primary efficacy endpoints included "Hand-to-floor" distance, pain intensity and Schober's test. The changes in "Hand-to-floor" distance between day 1 and day 3 and between day 1 and day 8 were compared between the two treatment groups using T-test for independent samples. ANCOVA was also used to adjust estimates for baseline values and clinical sites. The improvement in pain intensity between baseline (day 1) and each time point (days 2, 3, 4, 5, 6, 7), separately for movement, rest and sleep was compared between the two treatment groups using T-test for independent samples. ANCOVA was also used to adjust estimates for baseline values and clinical sites. The differences between baseline and each visit (day 3 and day 8) were also analyzed. At day 3 and day 8, the proportion of patients with negative Schober's test (i.e. measure ≥ 5 cm) was assessed and compared between treatment groups using Chi-square test. Logistic regression was used to estimate ORs adjusted for clinical sites. *Secondary endpoints* The difference in pain relief between the two treatment groups at day 3 and day 8 was assessed through Kruskal-Wallis Test. The difference in VAS score between the time of the second administration (Time 0) and each time point (minutes 30, 60, 90 and 180), on days 1, 2 and 3, was compared between treatment groups using T-test. ANCOVA was also used to adjust estimates for baseline values and clinical sites. Differences in Roland Disability Questionnaire at each visit with respect to baseline were estimated. T-test was used to assess differences in mean changes by treatment group at each time point. ANCOVA was also used to adjust estimates for baseline values and clinical sites. The differences in mean changes of Schober's test by treatment group between baseline and each time point were analyzed using T-test. ANCOVA was also used to adjust estimates for baseline values and clinical sites. The mean number of Paracetamol tablets used by patients as a rescue treatment for their low back pain was compared by treatment groups using T-test for independent samples. ANCOVA was also used to adjust estimates for baseline values and clinical sites. The proportion of patients that took at least one tablet of Paracetamol was compared between treatment groups using Chi-square test. Logistic regression was used to estimate ORs adjusted for clinical sites. *Safety endpoints* Adverse events were summarized as the number of patients with any AE, related AEs (including those possibly related, or not evaluable), and serious AEs. AEs were coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence, type, and severity of AEs were summarized in frequency tables according to the MedDRA terms. Chi-square test was be used to compare the frequency of patients with AE and the frequency and characteristics of AEs between treatment groups. Changes in vital signs between treatment groups were analyzed using T-test for independent samples.

Participant flow	237patients were screened and 236 were enrolled. 227 (96.19%) of the 236 enrolled patients completed the study: 113 (96.6%) in the Sirdalud® group and 114 (95.8) in the Tizaspray® group.
Recruitment	First subject enrolled: April 8th 2015 Last subject completed: January 31th 2017
Baseline data	Among the 234 patients included in the Safety population, 132 (56.4%) were females and 102 (43.6%) were males and there was no significant difference in the distribution of sex by treatment group. Mean age at Visit 1 was similar in the two treatment groups: 41.63 (SD=12.32) years old in the Sirdalud® group and 42.97 (SD=12.07) in the Tizaspray® group. All patients were Caucasian, except one black patient in the Tizaspray® group. The values for other characteristics were similar between treatment groups and there was not any statistically significant difference between treatment groups. At baseline, there was no difference between treatment groups in the primary endpoints (i.e., hand-to-floor distance, low back pain as measured by VAS and Schober's test)
Trial interruption	The trial was not interrupted.
Outcomes and estimation	**Efficacy results:** <u>*Primary endpoints*</u> *Hand-to-floor distance:* In the ITT population, the decrease in hand-to-floor distance observed in the Tizaspray® group was higher than that observed in the Sirdalud® group at Visit 2 (-7.20 vs. -4.27, p<0.01) and the difference increased at Visit 3 (-15.51 vs. -11.51, p<0.05). The difference between the two groups was statistically significant at both visits (p<0.001), when adjusted for baseline values and clinical sites. *Low back pain during visits:* In the ITT population, the decrease in average low back pain was more evident in the Tizaspray® group than in the Sirdalud® group already at Visit 2 (-18.48 vs. -14.27, respectively; treatment difference -4.21, p<0.05) and the difference between the two groups increased up to Visit 3 (treatment difference -9.26). The difference between the two groups was statistically significant at both visits when adjusted for baseline values and clinical site (p<0.01667 at Visit 2 and p<0.001 at Visit 3). The analysis of the three different low back pain measures (on movement, at rest and when sleeping) at Visit 2 and Visit 3 confirmed the higher improvement obtained with Tizaspray®. The decrease observed at Visit 3 was statistically significant for each measure, both with adjusted and unadjusted analysis. *Daily low back pain on movement, at rest and when sleeping:* The difference in the decrease in low back pain on movement between treatment groups was constantly increasing after Day 1 and it was statistically significant at Day 6 (p<0.01) and Day 7 (p<0.01667); when adjusted for baseline values and clinical sites, the significance level was p<0.001 on both these days. The difference in the decrease in low back pain at rest between treatment groups was also constantly increasing after Day 1 and statistically significant since Day 4 (p<0.05) and it climbed up to -9.11 (p<0.01) at Day 7, results confirmed by the adjusted analysis (p<0.001 at Day 7). The difference in the decrease in low back pain when sleeping was increasing after Day 2 and statistically significant since Day 6 (p<0.1667). The adjusted estimates gave statistically significant results since Day 4 (p<0.1667) *Schober's test:* In the ITT population, the proportion of patients negative to the Schober's test was slightly higher in the Tizaspray® group already at Visit 2 (day 3): 33% vs. 27.8%, but the difference was not statistically significant. At Visit 3 (Day 8) the proportion of patients negative to Schober's test in the Tizaspray® group was 73.7% and 59.6% in the Sirdalud® group, and chi-square test was statistically significant (p<0.05) . When adjusted for clinical sites, the logistic regression highlighted the outstanding significant protective effect of Tizaspray® against the Schober's test positivity (OR 0.35, 95% CI 0.17-0.73; p<0.01) The PP analysis confirmed the results of the ITT analysis.

Outcomes and estimation (continued)	<u>*Secondary endpoints*</u> *Pain relief:* In the ITT population, the pain relief is constantly better in the Tizaspray® group. In fact, at Visit 2, 53.1% of the patients in this group had a moderate to total pain relief against 42.6% in the Sirdalud® group. The proportions of patients with no pain relief were 18.3% and 2.6% in the Sirdalud® and Tizaspray® group, respectively, and the difference was statistically significant ($p<0.05$). At Visit 3, the proportions of patients with considerable to total pain relief were 74.6% and 49.1% in the Tizaspray® and Sirdalud® group, respectively, and the difference was statistically significant ($p<0.001$) *Short-term time course of low back pain intensity:* In the ITT population, the difference between the two treatment groups was already evident 30 minutes after treatment administration and grew up to 90 minutes. The differences were increasing day by day. The difference between treatment groups was statistically significant at 30 and 60 minutes after the study treatment administration on each day. At 90 minutes, at Day 1 only the unadjusted analysis was statistically significant ($p<0.05$), at Day 2 both analyses gave statistically significant results and at Day 3 only the adjusted analysis gave statistically significant results. The difference in low back pain registered 180 minutes after the study treatment administration was still slightly higher in the Tizaspray® group on Day 2 and Day 3. *Roland Disability Questionnaire (RDQ):* In the ITT population, the differences between treatment groups are in favor of the Tizaspray® at both visits and the differences are statistically significant ($p<0.05$ at Visit 2 and $p < 0.001$ at Visit 3) for both adjusted and unadjusted analysis *Schober's test (as a continuous variable):* In the ITT population, the difference between treatment groups was in favor of Tizaspray® and statistically significant at both visits ($p<0.001$), using both unadjusted and adjusted analysis. *Use of rescue medicine:* In the ITT population, the difference in the use of rescue medicine between treatment groups was in favor of the Tizaspray® group, in terms of mean number of tablets taken (1.68 less tablets taken). The difference was statistically significant when adjusted for clinical site ($p<0.05$). The proportion of patients that took the rescue medicine was lower in the Tizaspray® group (59.8% vs, 69.9% - OR = 0.58; p=0.0678).
Ancillary analysis	Not applicable
Adverse events	Only 18 patients out of 234 (7.69%) experienced at least an adverse event during the study. Six patients in the Sirdalud® group experienced globally ten AEs and twelve patients in the Tizaspray® group experienced globally twenty-one AEs. The proportion of AEs was similar between the two treatment groups for headache and somnolence. The patients treated with Tizaspray® experienced aphtous ulcer, nausea, hyperkalemia, burning sensation (1 event each) and nasal discomfort or pruritus (9events in 3 patients), events that did not occur in the Sirdalud® group. At the contrary, patients treated with Sirdalud® experienced fatigue, asthenia and disturbance in attention (1 event each), events that did not occur in the Tizaspray® group. Other differences were less relevant.
Trial termination	Study terminated prematurely YES☐ NO ☒

Discussion and interpretation of study results	The results of the study indicated the superiority of Tizaspray® 0.5 mg on the Sirdalud® 2 mg tablets treatment. Tizaspray® 0.5 mg appeared faster in its action than Sirdalud® 2mg tablets, according to the time course of pain intensity assessed after a single dose. Patients showed a more rapid decrease of pain intensity on days 1, 2 and 3 and the difference between treatment groups was statistically significant. This finding complies with the rate of absorption by IN observed in PK studies. Primary endpoints (physical ability as Hand-to-floor distance, pain as VAS difference, muscular contraction as Schober's test) resulted improved even in a statistically significant way already at Visit 2. Probably, there may be a relation between hourly effect on pain and daily effect on some markers of disease. The difference in primary endpoints is maintained up to Visit 3 (Day 8), even if a spontaneous improvement or resolution of the acute pathology was expected in both groups. The secondary endpoints confirmed the overall better efficacy of Tizaspray® 0.5 mg versus Sirdalud® 2 mg tablets. The use of paracetamol as a rescue medicine seems to be reduced in the group treated with Tizaspray®. The amount of paracetamol used was low and did not mask the efficacy of both treatments. The safety of Tizaspray® 0.5 mg resulted as good as that of Sirdalud® 2 mg tablets, except for specific adverse events at nasal mucosa. Laboratory tests and vital signs did not show any relevant difference between treatment groups: only 18 patients out of 234 experienced at least an adverse event. The AEs certainly correlated with Tizaspray® were those involving the nasal administration way, reported by two patients only. Concluding, the risk/benefit ratio of Tizaspray® 0.5 mg should be estimated considering the following considerations: - Tizaspray® 0.5 mg proved to be clinically superior to Sirdalud® 2 mg tablets - The number of systemic AEs related to Tizaspray® 0.5 mg was not higher than that observed using a clinically equivalent oral dose (2 mg) - Local AEs (nasal discomfort and pruritus) were manifested by less than 2% of patients administered with Tizaspray® 0.5 mg - unwanted risks of combined therapy are dramatically reduced avoiding the first pass effect - Paradoxical or overdose risks due to reduced hepatic or renal function are dramatically reduced because the single dose is a quarter of the oral dose.