A placebo-controlled, double-blind, randomized, trial of Diclofenac Gel AMZ001 3.06% for the treatment of knee osteoarthritis

NTC03691844

Document Date: 22Nov2018

1 Synopsis

Clinical Trial Protocol Number	AMZ001-006
Title	A placebo-controlled, double-blind, randomized, trial of Diclofenac Gel AMZ001 3.06 % for the treatment of knee osteoarthritis symptoms
Trial Phase	2/3
IND Number	116375
FDA covered trial	Yes
EudraCT Number	2018-001934-16
Sponsor	Amzell BV Chief Scientific Officer Name: Dario Carrara, PhD Address: Siriusdreef 22, Hoofddorp 2132WT The Netherlands
Sponsor Legal Representative in the European Union	Amzell BV Siriusdreef 41 Hoofddorp 2132WT The Netherlands Telephone Number: +31 23 55 60 460
Trial centers/countries	Denmark Czech Republic United States of America
Planned trial period (first subject in-last subject out)	First subject in: August 2018 Last subject out: March 2019
Objectives: Primary Objective • To evaluate changes in pain intensity, in terms of the WOMAC pain score of the target knee	

Secondary Objectives

- To evaluate changes in symptoms of OA
- To evaluate the changes in physical functioning
- To evaluate administration regimens of AMZ001
- To evaluate the safety and tolerability of AMZ001
- To evaluate changes in quality of life

Exploratory Objectives

- To finalize the validation of the pain diary and the satisfaction questionnaire
- To explore the onset of action of topical AMZ001
- To explore the efficacy of two regimens of AMZ001 and Voltaren® 1 % Gel
- To explore the level of diclofenac in plasma

Methodology:

This is a multicenter, randomized, double-blind, placebo-controlled, parallel group, 4-week trial of a novel formulation of diclofenac gel AMZ001 once or twice daily versus placebo twice daily, including a single-blind treatment group with commercial diclofenac 1 % (Voltaren®) gel four times daily. Approximately 440 subjects will be randomized to one of the four treatment groups. The subjects will be randomized with up to 120 subjects in each of the double-blinded treatment groups and up to 80 subjects in the single-blinded treatment group. The treatment groups are:

1. AMZ001 Diclofenac Gel 3.06 %, 2.3 grams (as two pump actuations of 1.15 grams), once in the morning, and placebo once in the evening, for each knee affected (total daily amount of diclofenac sodium per knee: 70 mg)
2. AMZ001 Diclofenac Gel 3.06 %, 2.3 grams, twice daily per knee affected (total daily amount of diclofenac sodium per knee: 141 mg)
3. Placebo Gel, 2.3 grams, twice daily per knee affected
4. Commercial Voltaren® 1 % gel, 4 grams, 4 times daily (single-blind) per knee affected (total daily amount of diclofenac sodium per knee: 160 mg)

After written informed consent is obtained, subjects will be screened for eligibility. At the Screening Visit, subjects will first undergo a medical history interview to verify that they meet demographic and clinical criteria for inclusion into the study. Subjects will self-evaluate pain, after adequate wash out of any pain medication, on a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain sub-score (5 questions) questionnaire for both knees and hips. If both knees meet radiographic and pain criteria, the reported pain score of the target knee should exceed that of the contralateral knee. If hip pain of either hip exceeds that of the target knee, the subject should be discharged from the study.

A physical examination including vital signs, measurement of sitting diastolic and systolic blood pressure, heart rate, and measurement of height and weight will be performed. Subjects not meeting the defined criteria will be discharged from the study.

X-ray images of the knees will be obtained using a Fixed-Flexion frame (Synaflexor© or similar) and a central radiologist reader will grade osteoarthritis on the Kellgren-Lawrence scale.

Blood will be collected for hematology and safety chemistry. A screening serum pregnancy test will be performed for subjects who are women of child-bearing potential.

Upon meeting all eligibility criteria and completing all screening assessments, a target knee will be assigned and subjects will be randomized into one of four groups. Presence of bilateral OA of the knees is allowed. If both knees fulfill the diagnostic, radiographic, and symptomatic inclusion criteria, both knees should be treated with IMP throughout the treatment period, but the more painful knee is selected as the target knee. If significant pain, defined as meeting the pain inclusion criteria 5 and 7, of the contralateral knee arises during the course of the trial, IMP treatment should be initiated on the contralateral knee in addition to the target knee, and continued on both knees through the remainder of the trial. Initiation of treatment of the contralateral knee should only be initiated at study visits, and not between study visits.

The treatment phase consists of four weeks of treatment with one baseline (Day 1) visit and 4 weekly visits, in addition to performing daily Pain Diaries and WOMAC pain sub-score (5 questions) questionnaires at home during the first week of treatment in the evening of every day. One final follow-up phone visit will be performed approximately 14 days after the last IMP application has been performed.

WOMAC, Intermittent and Constant Osteoarthritis Pain (ICOAP) and other questionnaires will be performed on Days 1 (Baseline), 8, 15 and 22 and 29. In order to “washout” the effect of rescue medication, the subjects should refrain from taking rescue medication within 12 hours prior to any study visit.

Subjects will apply IMP gel on the painful target knee joint in accordance with the allocated treatment group. At each planned dispensation of study drug (Day 1 and Day 15):

- The subjects in the double-blinded groups (treatments 1, 2 and 3) will be provided with two (2) metered dose dispensers of gel, each marked for either morning or evening use.
- The subjects in treatment 4 will be provided with 5 tubes of Voltaren® 1% gel.

Table 1: Application Schedule

	AMZ001 Diclofenac Gel 3.06 % QD[1]		**AMZ001 Diclofenac Gel 3.06 % BID[1]**		**Placebo[1]**		**Voltaren® 1 % gel[2]**
	Active	Placebo	Active	Placebo	Active	Placebo	
Morning	**X**		**X**			**X**	**X**
Noon	N/A	N/A	N/A	N/A	N/A	N/A	**X**
Evening		**X**	**X**			**X**	**X**
Bedtime	N/A	N/A	N/A	N/A	N/A	N/A	**X**

[1]Two pump actuations of each 1.15 gram of gel to be applied per treated knee at each application

[2]Four grams of gel to be applied per treated knee at each application

Planned number of subjects:

Up to 440 subjects. 120 will receive AMZ001 once daily and placebo once daily, 120 will receive AMZ001 twice daily, and 120 will receive placebo twice daily. A single blinded group of 80 subjects will receive Voltaren® 1 % gel 4 times daily.

Primary endpoint (double-blind treatment group only):

The primary endpoint of this trial is the change from baseline in WOMAC pain sub-score (questions 1 to 5) in the target knee as evaluated at week 4.

Secondary endpoints (double-blind treatment group only):

- Changes from baseline in WOMAC total score and the WOMAC function and stiffness scores at week 4
- Changes from baseline in constant and intermittent OA pain assessed by ICOAP scores at week 4
- Changes from baseline in WOMAC pain weight-bearing score (questions 1, 2, and 5) and non-weight bearing score (questions 3 and 4) at week 4
- Changes from baseline in physical function assessed by the chair-stand test at week 4
- OMERACT-OARSI responder rate at week 4
- Total dose of rescue medication calculated as the sum of tablets used, based on pill counts
- Time between baseline and first use of rescue medication
- Change from baseline in WOMAC pain sub-score (questions 1 to 5) between groups receiving AMZ001 QD and BID in the target knee as evaluated at week 4
- Changes from baseline in constant and intermittent OA pain assessed by ICOAP scores between groups receiving AMZ001 QD and BID at week 4
- Changes from baseline in WOMAC pain weight-bearing score (questions 1, 2, and 5) and non-weight bearing score (questions 3 and 4) between groups receiving AMZ001 QD and BID at week 4
- Changes from baseline in physical function assessed by the chair-stand test between AMZ001 QD and BID at week 4
- Changes from baseline in WOMAC total score and the WOMAC function and stiffness scores between AMZ001 QD and BID at week 4.
- Changes from baseline in the impact of OA on daily living as assessed by the Patient Global Assessment (PGA) score at week 4

- Changes from baseline in work productivity and activity assessed by the WPAI at week 4

- Changes from baseline in quality of life assessed by the EQ5D at week 4

Exploratory endpoints and safety and tolerability endpoints are discussed in Sections 8.3.4 and 8.3.3 of the protocol, respectively.

Diagnosis and inclusion and exclusion criteria:

Inclusion Criteria:

1. Subject is able to read and understand the language and content of the study material, understand the requirements for study visits, and is willing to provide information at the scheduled evaluations and appropriate written informed consent has been obtained.
2. Femorotibial osteoarthritis of the knee, according the American College of Rheumatology (ACR) clinical and radiographic criteria (Altman et al. 1986) (Appendix A).
3. Radiological OA grade 1, 2, or 3 of the target knee, using the Kellgren-Lawrence method (KELLGREN & LAWRENCE 1957) as graded by central, independent reading of X-ray obtained during screening, or on a recent (within 6 months) X-ray image which fulfills the specifications for central reading.
4. Age between 40 years and 85 years at the time of screening, both included; of either sex.
5. Pain score rated on an 11-point numerical rating scale of the target knee of ≥ 20 and ≤ 45 out of 50 in response to the WOMAC pain sub-score (5 questions), at the time of screening. The subject should have undergone a washout-period of at least 5 half-lives of any analgesic medication before completing the screening questionnaire.
6. Women of child-bearing potential must use at least an acceptably effective method of contraception (progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, cap, diaphragm or sponge with spermicide). Postmenopausal status is defined as being amenorrheic for at least 1 year prior to screening. Sexually active men with a female partner of childbearing potential must agree to use condom from enrolment up to at least 3 months after the study end.
7. Knee pain in the target knee for 14 days of the preceding month (periarticular knee pain due to OA and not due to non-OA conditions such as bursitis, tendonitis, etc.) based on subject report.
8. On stable pain therapy (i.e., at least 3 days per week for the previous month) with an oral NSAID, or acetaminophen/paracetamol prior to the Screening Visit.
9. Except for osteoarthritis, the subject is in reasonably good health as determined by the Investigator.

Exclusion criteria:

1. Known or suspected hypersensitivity to or previous hypersensitivity reactions to diclofenac, other non-steroidal anti-inflammatory drugs or related substances including aspirin, any of the excipients in either of the investigational products, or any physical impediment to gel application on the target knee.
2. Intra-articular delivery of corticosteroids or hyaluronic acid in the target knee within 6 months of screening or into any other joint within 30 days of screening.

3. High dose (equivalent to > 5 mg of prednisone/day) systemic corticosteroid treatment of more than 14 days during the past 6 months prior to screening.
4. Major surgery or arthroscopy of the target knee within the previous year prior to screening.
5. Planned surgery of the target knee within the next 3 months.
6. Use of a currently unapproved investigational drug, device or biologic within 6 months prior to screening.
7. Presence of concomitant non-osteoarthritic disease affecting either knee, such as rheumatoid arthritis, psoriasis, gout or pseudogout, if there is reason to believe that the disease(s) may significantly interfere with the interpretation of the clinical response to the study drug.
8. Medical history of coronary artery bypass graft surgery.
9. Current malignancy or treatment for malignancy within the past five years, with the exception of non-melanoma skin cancer, unless affecting the target knee area, or carcinoma in situ events.
10. Any other abnormal laboratory results or significant medical conditions that the Investigator believes should preclude the subject's participation in the trial.
11. Secondary osteoarthritis of the target knee, previous procedures or trauma affecting joint homeostasis including total meniscectomy or septic arthritis, or any other serious condition leading to secondary OA of the target knee.
12. Reported incidence of any of the following diseases: known osteoarthritis of the hip(s) if pain in either or both hip(s) exceeds that of the target knee using the WOMAC Hip Pain sub-score, presence of significant radicular back pain, or at least one migraine attack within the past 12 months before screening, as reported by the subject.
13. Presence of severe pain in either knee, defined as > 45 out of 50 in response to the WOMAC pain sub-score (5 questions), at the time of screening, regardless of the eligibility of the contralateral knee.
14. Body Mass Index > 45.0 kg/m^2.
15. Estimated glomerular filtration rate < 30 mL/min using the Modification of Diet in Renal Disease (MDRD) method.
16. Generalized skin irritation, previous skin reactions upon use of topical NSAIDs, current skin irritation or redness at the planned site of gel application, or significant skin disease including psoriasis, as judged by the investigator.
17. Known presence of gastroduodenal ulcer or any gastrointestinal bleeding (except hemorrhoidal) within 6 months prior to screening.
18. Use of any topical medication on the planned application site within 15 days of the time of randomization.
19. Use of moderate or higher doses of opioid medication for the treatment of pain within 6 weeks before the screening visit.
20. Use of duloxetine, pregabalin, or gabapentin within 4 weeks before the screening visit.
21. History of alcohol or drug abuse within the past year prior to randomization.

Investigational Medicinal Products:

Double-blind therapy:

Diclofenac Sodium 3.06 % (AMZ001) gel or matching placebo gel in an 87 g metered dose dispenser, 2.3 grams of gel to be applied twice daily (morning and evening).

Single-blind therapy:

Single-blind comparator: Voltaren® (diclofenac sodium) 1 % gel in a 100 g tube, 4 grams of gel to be applied four times daily.

Rescue medication:

Paracetamol tablets 500 mg. The dosage of acetaminophen/paracetamol that the subjects will be allowed to take per day will be defined according to the standard of care in the countries where the trial will be carried out; however, the maximum dose should not exceed 1 gram per dose and 4 grams per day.

Planned trial and treatment duration per subject:

The treatment phase consists of four weeks of treatment with one baseline (Day 1) visit and 4 weekly visits, followed by a follow-up visit two weeks after last application of IMP. The screening period is up to 21 days from the time of providing written consent. In total, the expected duration of the trial participation of a randomized subject will be up to 63 days.

Statistical methods:

Treatment effect of the primary endpoint of change from baseline in WOMAC pain sub-score will be based on a repeated measures ANOVA model including the baseline value, the treatment group, the visit, and treatment by visit as interaction. Comparison of AMZ001 gel versus placebo will be performed within the context of this model. The difference and the corresponding 95% confidence interval (CI) and p-value will be presented. The same ANOVA model used for the primary endpoint will be used to assess the treatment effect of the secondary endpoints. The significance level will be set at 5 % two-sided, and p-values will not be adjusted for multiple comparisons.

The power is determined from expected changes in the primary endpoint of the change from baseline in pain as evaluated by the WOMAC pain sub-score. The power calculation is based on data from a 4-week double-blind diclofenac sodium 2 % topical solution treatment study in knee osteoarthritis patients (Wadsworth et al. 2016). In this study using the WOMAC LK 3.1 scale (0-4 for each question), a decrease from baseline in WOMAC pain sub-score (5 questions)

was recorded in the diclofenac treatment group of 4.5 (SD 4.5) and in the placebo group 3.6 (SD 4.2).

The estimated common SD of 4.4 in the LK 3.1 scale can be converted to a SD of 4.4 * 2.5 = 11 in the NRS scale. With the assumptions of the SD of 11 (NRS scale), 120 subjects enrolled in each of the double-blinded treatment arms, 10 % dropout rate, normal distribution, 5 % level of significance two-sided, 80 % power, the study will be powered to detect a treatment difference in WOMAC pain sub-score between AMZ001 BID and placebo of 4.2 on the NRS scale.

Table 2: Schedule of Trial Procedures

Activity/Assessment	Screening 1a[1]	Screening 1b[1]	Baseline V2	On Treatment Visits V3	V4	V5	V6	14-Day Safety Follow-up[2] V7
Study Week	-	-	0	1	2	3	4	6
Study Day	-21 to - 5	-13 to -1	1	8	15	22	29	43
Visit Window (days)	-	-	0	+/- 2	+/- 2	+/- 2	+/- 2	+/- 5
Informed Consent	X							
Medical history	X							
Inclusion/exclusion criteria	X	X	X					
Demographic data	X							
Physical examination	X						X	
Skin Tolerability Assessment			X[3]	X	X	X	X	
Knee X-ray (both knees)	X							
Instructions on reporting pain[4]	X							
WOMAC Questionnaire [5,6,7]		X	X[5]	X	X	X	X	
ICOAP Questionnaire [6]			X	X	X	X	X	
Pain Diary[8]			X[8]	X[8]	X[8]	X[8]	X[8]	
Patient Global Assessment			X	X	X	X	X	
WPAI			X	X	X		X	
EQ5D			X			X	X	
Satisfaction questionnaire					X		X	
Chair-stand test[6]			X		X		X	
Selection of target knee			X					
Height and weight	X						X[9]	
Blood pressure and heart rate	X		X	X	X	X	X	

Activity/Assessment	Screening 1a[1]	Screening 1b[1]	Baseline V2	On Treatment Visits V3	V4	V5	V6	14-Day Safety Follow-up[2] V7
Study Week	-	-	0	1	2	3	4	6
Study Day	-21 to - 5	-13 to -1	1	8	15	22	29	43
Adverse events	X[10]	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Randomization			X					
Study drug dispensation and weighing of kit(s)			X		X[15]			
Dispensation of IMP "instructions for use" pamphlet			X		X			
Instruction of study drug application and frequency of use			X					
Application of morning study drug on site under staff supervision			X	X	X	X	X	
Weighing of kit(s) for compliance assessment				X	X	X	X	
Rescue medication dispense			X		(X)[11]	(X)[11]		
Rescue medication collection[12]					(X)[11]	(X)[11]	X	
12 lead ECG	X						X	
(Rescue) Analgesic Wash-out		X	X	X	X	X	X	
Hematology	X			X	X	X	X	
Safety chemistry and urine dipstick	X			X	X	X	X	
Pregnancy test[13]	X		X		X		X	
Blood sample for plasma level of diclofenac [14]					X		X	

EQ5D: EuroQol-5 Domain. ICOAP: Intermittent and Constant Osteoarthritis Pain. WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index. WPAI: Work Productivity Activity Index.

1. If subject is washed out of analgesics at Screening Visit 1a, the examinations scheduled for screening visits 1a and 1b can be performed on the same day.

2. Phone call.
3. Skin assessment to be performed prior to application of study drug at baseline visit.
4. Subjects will be educated on appropriate expectations around their participation in a clinical study and the importance of reliably consistently and accurately reporting their pain throughout the study.
5. WOMAC pain sub-score (5 questions) to be assessed on a daily basis on paper at home during first week of treatment, i.e. the period between Visit 2 and Visit 3.
6. Assessed without analgesic medication for five half-lives of the analgesic.
7. WOMAC assessment of hips should only be performed at the screening visit.
8. To be completed daily in the evening during the first week of treatment, i.e. between Visit 2 and Visit 3. In the period between other subsequent visits, the questionnaire will be completed during the evening of the day prior to the next visit.
9. Only weight collected.
10. Conditions previously unknown to the subject at the time of the screening visit will be recorded as medical history. All subsequent events will be recorded as adverse events.
11. To be collected/dispensed if previously dispensed supply of rescue medication was depleted and empty packaging returned to site.
12. Collection of remaining rescue medication at Visit 6. Empty packaging of previously dispensed kit should be returned to the site if new rescue medication is requested.
13. Serum test at screening visit, urine dipstick at all other visits.
14. To be done after IMP application and questionnaire/test completion (approximately 1-2 hours after IMP application). Exact time of IMP application and time of blood sampling must be documented.
15. Dispensation is not mandatory for subjects allocated to Voltaren®gel