A Phase 2 Double-Blind Clinical Trial to Examine the Comparative Effects on Osteoarthritic Knee Pain of CGS-200-1 (1% Capsaicin Topical Liquid), CGS-200-5 (5% Capsaicin Topical Liquid), and CGS-200-0 (Vehicle, No Capsaicin) – Protocol

Protocol Number: VZU00025

Protocol Date: 1-AUGUST-2018

NCT03528369

Protocol Title: A Phase 2 Double-Blind Clinical Trial to Examine the Comparative Effects on Osteoarthritic Knee Pain of CGS-200-1 (1% Capsaicin Topical Liquid), CGS-200-5 (5% Capsaicin Topical Liquid), and CGS-200-0 (Vehicle, No Capsaicin)

Protocol Number: VZU00025

Version No./Date: 5.0 / 1-AUGUST-2018

Study Drug: CGS-200-5 (Capsaicin 5% Topical Liquid);
CGS-200-1 (Capsaicin 1% Topical Liquid); and,
CGS-200-0 (Investigational Drug Product Vehicle, 0% Capsaicin)

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Confidential and Proprietary

Investigator Agreement

I confirm that I have read and understood this protocol and agree to conduct this study as outlined in the protocol and other information supplied to me. I agree to conduct this study in compliance with Good Clinical Practice (GCP) standards as defined by the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice, the ethical principles of the Declaration of Helsinki, all applicable national, state and local regulations, as well as the requirements of the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and any other institutional requirements.

Principal Investigator:

_____

Signature *Date*

_____

Name (please type or print)

_____

Institution

_____

Address

STUDY SYNOPSIS

Sponsor:	Vizuri Health Sciences LLC 12500 Fair Lakes Circle Suite 450 Fairfax, VA 22033
Protocol Title:	A Phase 2 Double-Blind Clinical Trial to Examine the Comparative Effects on Osteoarthritic Knee Pain of CGS-200-1 (1% Capsaicin Topical Liquid), CGS-200-5 (5% Capsaicin Topical Liquid), and CGS-200-0 (Vehicle, No Capsaicin)
Protocol Number:	VZU00025
Study Phase:	Phase 2
Study Endpoints:	The **Primary Efficacy** endpoint of this study will be to examine the extent of reduction in the WOMAC pain score, relative to baseline, provided by once daily, one-hour application of Vehicle (CGS-200-0), CGS-200-1, and CGS-200-5 at the following assessment times: Baseline: $\leq$ 30 minutes prior to first daily application Day 35 31 Days (+/- 3 days) after fourth daily application and based thereon to determine whether the responses for treatment with CGS-200-1 and CGS-200-05 are significantly different from Vehicle (CGS-200-0) and from each other at the primary endpoint time. The **Primary Safety** endpoints will be: (1) The application of the study drug does not produce skin reactions (erythema, scaling, pruritus, or other) to a degree that is clinically of concern. Scoring of erythema and scaling at the application sites and of pruritus will be assessed per the scoring systems in Appendix F. (2) No SAE's either possibly, probably, or definitely associated with study treatments. (3) Safety labs (hematology, serum chemistry and urinalysis) do not produce other than minimal – mild toxicities (Grade 1 or Grade 2). Scoring of clinical, hematological and urinalysis out of range findings for toxicity grading will be per Appendix B.

STUDY SYNOPSIS (continued)

	Secondary Efficacy endpoints will be: (1) To examine the extent of reduction in the WOMAC pain score, relative to baseline, provided by once daily, one-hour application of Vehicle (CGS-200-0), CGS-200-1 and CGS-200-5 at the following assessment times: Baseline: ≤ 30 minutes prior to first daily application Day 5 24 hrs (+/- 3) after last of the 4 daily applications Day 19 15 days (+/- 3) after last of the 4 daily applications Day 64 60 days (+/- 3) after the last of 4 daily applications Day 94 90 days (+/- 3) after the last of 4 daily applications (2) Day 5, 19, 35, 64, and 94 WOMAC scores on the stiffness and function subscales as well as total WOMAC score (including the WOMAC pain score). **Secondary Safety** endpoints will be: (1) The distribution by study arms of specific Adverse Events (AEs) (e.g., local application site reactions, and other AEs (inclusive of findings for hematology and serum chemistry)). (2) Evaluate the amount of concomitant pain medications used overtime **Tolerability** endpoints (which are secondary in nature) will be: (1) The application of study drug does not produce burning-stinging pain ("BSP") at the application site to a degree that is not acceptable to the subject. BSP at the application site, this will be assessed using a 0 – 10 NRS scale without guideposts. "Acceptability" of BSP will be queried per subject at the end of each application period. (2) The application of the study drug does not produce pruritus during application or in the 24 hrs post-application to a degree that is not acceptable to the subject or, if bothersome to the subject, cannot be managed by application of ice or a cold pack or compress

STUDY SYNOPSIS (continued)

Study Duration	13-14 weeks for each subject, excluding screening.
Study Design:	This is a multi-center, randomized, double-blind clinical trial in subjects with OA according to the 1986 American College of Rheumatology (ACR) criteria. There will be with three study arms: Arm 1 CGS-200-0 (Investigational Drug Product Vehicle) Arm 2 CGS-200-1 (1% Capsaicin in CGS-200 vehicle) Arm 3 CGS-200-5 (5% Capsaicin in CGS-200 vehicle) Each Arm will enroll 40 evaluable subjects, for a total of 120 evaluable subjects in this study. Subjects that give Informed Consent to participate and who are deemed after screening to be eligible to participate will be randomized to one of the three study Arms. Subjects will receive the Arm-appropriate treatment as a topical application over the frontal aspect of the knee(s) once daily on four consecutive days. The applications will be at the clinic but by the subject under supervision of clinic personnel. Wearing gloves supplied by the clinic staff, the subject will apply the study drug on and around the knee covering a 10cm by 10cm area. The application will be left in place for 60 (up to 65) minutes and then washed off at the clinic by clinic personnel. The amount of Investigational Drug Product to be applied is estimated to be approximately 0.13 mL based on experience in prior studies. Even though both knee(s) will receive application of study test materials, with regard to reduction in WOMAC pain and VAS pain score associated with study treatments, only one knee will be indicated as the "Study Knee". This will be the knee with the highest WOMAC pain score at baseline. If both knees have equal WOMAC pain scores at baseline, then the right knee will be considered the "Study Knee" with regard to WOMAC pain and VAS pain score reduction. The Investigators, all site staff, study subjects and Clinical Research Organization (CRO) personnel (except for the Medical Monitor providing safety oversight) directly involved in the study will remain blinded to the treatment assignment throughout the trial.
Estimated No. of Subjects:	Total 120 evaluable subjects: 40 subjects will be allocated to each study Arm. An allowance of up to 10 subjects per Arm is to be provided for dropouts whose withdrawal is not due to lack of study drug tolerability).

STUDY SYNOPSIS (continued)

Inclusion/Exclusion Criteria:	**Inclusion Criteria** The subject must meet all of the following: 1. Able to comprehend the informed consent form (ICF) and provide Informed Consent, and capable of complying with all study procedures; 2. Male or female, 35 years of age to 75 years; 3. OA of at least one knee according to 1986 ACR Classification Criteria; 4. OA of at least one knee must be confirmed by tibiofemoral joint radiographs obtained within the past 6 months; 5. Rheumatoid factor (RF) negative and Erythrocyte sedimentation rate (ESR) <40 mm/hr; 6. Chronic knee pain in at least one knee for $\geq$ 3 months; 7. WOMAC pain score of $\geq$ 250 (using VAS WOMAC format) at screening, and at baseline, in at least one knee; 8. Knee pain score of $\geq$ 5 on the NRS pain scale at screening, and at baseline, in at least one knee; 9. Knee pain is not potentially due to acute trauma unrelated to OA (no acute traumatic knee injury in medical history); 10. No burning-stinging pain, unrelated to subject's knee pain, at intended site of application; 11. Knee pain must be greater than pain in any other part of subject's body; 12. ACR global functional status I, II, or III (excluding IV); 13. If female, subject must be past childbearing age or otherwise must test negative for pregnancy. Males and females must agree to use effective birth control for at least 30 days after last dose of study drug. **Exclusion Criteria** The subject must not have any of the following: 1. Spontaneously improving or rapidly deteriorating OA of the knee; 2. Rheumatoid or psoriatic arthritis, or a form of arthritis (e.g. gout, pseudogout), Paget's disease of bone, or any other disease affecting the joints that are inconsistent with a diagnosis of idiopathic OA; 3. Use of topical, oral, or injectable steroids for 1 month prior to screening, or intraarticular visco-supplementation within 3 months prior to screening; 4. Used any capsaicin-containing product on or in the vicinity of the knee within 4 weeks prior to screening;

STUDY SYNOPSIS (continued)

	5. Used topically applied products (including emollients or moisturizers) on or in the vicinity of the knees or shaved the knees within 2 days prior to the first application of study drug; or an open wound near the knee; cutaneous erythema or edema; any inflammatory skin lesions such as eczema or psoriasis; cutaneous infections; or any other compromise of the skin; 6. A history of sensitivity to topical substances inclusive of OTC topical analgesics; 7. Labile or poorly controlled hypertension; 8. Significant cardiovascular, renal, or other diseases or conditions, or laboratory or other test abnormalities that, in the opinion of the Investigator, would contraindicate participation in the trial; 9. A psychiatric disorder or significant anxiety or depression that could interfere with the subject's compliance with study procedures or completion of the study; 10. Requires daytime use of medications or substances (alcohol, benzodiazepines, barbiturates, muscle relaxants, tranquilizers, hypnotics) that could diminish their cognitive ability to comply with study procedures; 11. A history of drug or alcohol abuse within one year prior to screening; 12. Requires or anticipates any surgical procedure within 3 months prior to screening, has had surgery on the affected joint within 6 months prior to screening, has a prosthesis in either knee , or would require surgery while participating in the trial; 13. Pregnant or nursing; 14. Treated with an investigational drug, device or therapy within 30 days prior to screening. 15. Body mass index greater than 45 kg/m^2 16. Skin on or near knee is broken or damaged or if there is an open wound on or near the knee.
Investigational Product and Mode of Administration:	CGS-200-1 and CGS-200-5 are topical analgesic liquids intended for application to intact, non-irritated skin in adults with musculo-skeletal pain inclusive of OA of the hands, wrists, elbows, or knees for the relief of pain, reduction of stiffness, and increased functional activity. CGS-200-1 is a multi-component formulation in which the active ingredient for the intended therapeutic effect is 1% capsaicin (wt/wt). CGS-200-5 is a multi-component formulation in which the active ingredient for the intended therapeutic effect is 5% capsaicin (wt/wt). Placebo for this study is the vehicle (designated CGS-200-0) which has no capsaicin.

STUDY SYNOPSIS (continued)

Study Monitoring	This study will be monitored by CRO personnel. An electronic case report form (eCRF) will be used for this study
Statistical Analysis	**Primary Efficacy Endpoint** The group mean LMS difference between each Active Treatment Arm and the Vehicle Arm for the WOMAC pain score at Day 35 will be tested for significance of difference at a significance value of $p \leq 0.05$. **Secondary Efficacy Endpoints** The group mean LMS difference between each Active Treatment Arm and the Vehicle Arm for the WOMAC stiffness, function and total score at Days 5, 19, 35, 64, and 94 will be tested for significance of difference at a significance value of $p \leq 0.05$. Also, the group mean reduction in OA knee pain score on a 100 mm VAS scale for each active treatment arm will be compared to the vehicle arm and tested for significance of difference at a significance value of $p \leq 0.05$. For dose-response estimation: The group mean LMS difference between the 5% and the 1% Active Treatment Arms for the WOMAC pain, stiffness, function and total score at Day 35 will be tested for significance of difference at a significance value of $p \leq 0.05$. **Primary Safety Endpoint** This will be analyzed using descriptive statistics in tabular form. **Secondary Safety Endpoint** This will be analyzed using descriptive statistics in tabular form. **Tolerability Endpoint** This will be analyzed using descriptive statistics in tabular form. **Other** Sponsor may elect to conduct appropriate post-hoc analyses.

SIGNATURE PAGE

Product name: **CGS-200-1 (Capsaicin 1% Topical Liquid)**
CGS-200-5 (Capsaicin 5% Topical Liquid)
CGS-200-0 (Vehicle, 0% Capsaicin, placebo)

Protocol Number: **VZU00025**

The signatures of the representatives below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol, including all statements as to confidentiality. It is also agreed that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

Internal personnel (Vizuri Health Sciences LLC):

[redacted]
Chief Scientific Officer
Head of Regulatory Affairs

Signature _____ Date _____

[redacted]
Independent Clinical Operations Consultant

Signature _____ Date _____

STUDY SYNOPSIS (continued)

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event
ALK	Alkaline phosphokinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BP	Blood pressure
BPM	Beats per minute
BSP	Burning stinging pain
BUN	Blood urea nitrogen
C	Celsius
CBC	Complete blood count
CHO	Chinese Hamster Ovary
cm	Centimeter
C_{max}	Maximum concentration in serum
CNS	Central Nervous System
CPK	Creatine phosphokinase
CRO	Contract Research Organization
dL	Deciliter
DLT	Dose-limiting toxicity
DR	Dominican Republic
ECG	Electrocardiogram
eCRF	Electronic case report form
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FSH	Follicle-stimulating hormone
FOB	Functional Observation Battery
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
Hgb	Hemoglobin
HPLC	High-performance liquid chromatography
hr	Hour
HR	Heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LSM	Least Mean Squares
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mg	Milligram

LIST OF ABBREVIATIONS (continued)

min	Minute
mITT	Modified Intent-to-Treat
mL	Milliliter
µL	Microliter
mm	Millimeter
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OAKP	Osteoarthritis knee pain
OTC	Over the counter
PE	Physical examination
PI	Principal Investigator
RBC	Red blood cell
RCTC	Rheumatology Common Toxicity Criteria
RDC	Remote data capture
RF	Rheumatoid factor
RR	Respiratory rate
SAE	Serious adverse event
SAF	Safety
SF	Synovial fluid
SOP	Standard Operating Procedure
T	Temperature
TEAE	Treatment-emergent adverse event
TFM	Tentative Final Monograph
T_{max}	Time to maximum effect
UA	Urinalysis
UCL	Upper confidence limit
ULN	Upper limit of normal
U.S.	United States
VAS	Visual Analog Scale
WBC	White blood count
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Index of Osteoarthritis
wt	Weight

1.0 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

The prevalence of arthritis in the general population is 21% overall, or approximately 46.4 million adults in the United States (U.S.).[1] Most of individuals are likely to have osteoarthritis (OA), which is a very common disease. It is the third most common diagnosis made by primary care physicians in older patients and is the most common condition involving the knee. Significant knee pain affects about one quarter of the population that are 55 or older, and half of these individuals have radiographic evidence of OA and a quarter have some degree of disability. The risk of developing OA is related to advancing age, female sex, obesity, trauma, a family history and other factors.

In 1986, the American College of Rheumatology (ACR) published classification criteria for OA of the knee.[2] Classification criteria are not diagnostic criteria, although they are often used as such by clinicians. The criteria are useful in clinical research, including clinical trials, to provide a uniform population for study. The classification criteria are shown in the table below.

Clinical and laboratory	Clinical and radiographic	Clinical
Knee pain + At least 5 of 9: Age >50 years Stiffness <30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth ESR <40 mm/hr RF <1:40 Synovial fluid signs of OA	Knee pain + At least 1 of 3: Age >50 years Stiffness <30 minutes Crepitus + Osteophytes	Knee pain + At least 3 of 6: Age >50 years Stiffness <30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth

ESR = Erythrocyte sedimentation rate; RF = rheumatoid factor; Synovial fluid (SF) signs of OA are clear, viscous fluid or SF white blood cell count <2,000/mm^3

The European League Against Rheumatism (EULAR) has developed guidelines for the diagnosis of OA.[3] During the development of the guidelines, they found that 3 symptoms (persistent knee pain, morning stiffness, and decreased function) and 3 signs (crepitus, restricted movement, and bony enlargement) were most important in the diagnosis. The more symptoms and signs, the more certain is the diagnosis. While diagnostic guidelines are useful in patient care, it will be necessary to use classification criteria in this clinical trial.

The pathogenesis of OA remains unclear; however, certain types of OA show familial aggregation, and excessive load on joints may play a role. In addition, over the years, there has been some consideration as to whether OA involves inflammation and whether it is a primary driver of the development of OA or whether trauma or other factors produce damage that results in secondary inflammation.

Whatever the pathogenetic mechanisms may be, OA is a progressive disorder that results in disability. There is a great unmet medical need for more effective treatments for OA. Better treatment of the pain of OA has the potential for postponing disability and improving health-related quality of life

Current standard of care for OA may include non-pharmacologic interventions such as exercise, weight loss, appropriate insoles, walking aids, patellar taping in a medial direction, thermal treatments, tai chi, psychosocial interventions and self-management programs.[4] Pharmacologic agents that can be used include acetaminophen, non-steroidal anti-inflammatory drugs (NSAID) given orally or topically, tramadol, duloxetine, and intra-articular hyaluronate, corticosteroids, or injections. In addition, opioids may be considered in those who respond inadequately to initial interventions. In patients who have failed medical therapy or are not willing to undergo surgery, or for whom joint replacement surgery is contraindicated, opioid therapy is strongly recommended.

Acetaminophen carries a risk of liver damage. The use of oral NSAIDs is associated with a potential for gastric and intestinal ulceration and high doses of NSAIDs have been associated with an elevated risk of cardiac problems. The intent of topical NSAIDs is to reduce the systemic levels of these drugs (thereby lowering the risk of gastro-intestinal damage) while providing for a therapeutically effective level in and around the affected area. However, these products – whether oral or topical – require regular daily use and administration more than once daily. The use of any opiate-containing product poses a risk for addiction or diversion.

There is therefore considerable unmet medical need for a treatment of OA knee pain (OAKP) that does not require regular daily use, does not carry the gastro-intestinal risks of NSAIDs or the liver risks of acetaminophen or the addiction / diversion risks of opiates, and can safely provide long lasting pain relief after a brief course of treatment.

Sponsor's experience suggests that capsaicin, a principal active component in chili peppers, may provide extended analgesia for OAKP after topical treatment.

In a prior study with over-the-counter (OTC) strength topical capsaicin (0.25%) in the CGS-200 vehicle (Study VZU00022), it was noticed that the placebo effect for the vehicle control itself resulted in subject response rates of 20% to 25% of subjects attaining > 50% pain score reduction over the first four days of daily once-a-day application (using the 100 mm Visual Analog Scale (VAS) for pain assessment). In the same study, twice daily application of CGS-200 vehicle resulted in subject response rates (i.e.: > 50% pain score reduction) of from 20% to 40% over the first four days of treatment. The vehicle control response rates in VZU00022 are tabulated below:

Study Arm	24 hrs after 1st Appl.	24 hrs after 2nd Appl.	24 hrs after 3rd Appl.	24 hrs after 4th Appl.
Once Daily	20.00%	20.00%	25.00%	25.00%
Twice Daily	20.00%	30.00%	35.00%	40.00%

The maximum mean placebo response rate after completion of 7 daily treatments (once or twice daily) was 28.67% for once daily and 39.21% for twice daily.

In another previous study (VZU00021), CGS-200 with 5% capsaicin ("CGS-200-05") and CGS-200 with 10% capsaicin ("CGS-200-10") both provided a very high response rate (i.e.; 80% - 90% with > 50% reduction in the Numerical Rating Scale (NRS) pain score after just 2 once daily applications), much higher than the response rate for vehicle in Study VZU00022. Study VZU00021 was neither vehicle or placebo controlled.

However, in yet another previous study (VZU00023) the response rate for vehicle was essentially the same as for CGS-200-05 (i.e.: 80% - 90% reduction in NRS pain score). [redacted]

Both VZU00021 and VZU00023 were conducted in the Dominican Republic ("DR", under approval from the national authority [CONABIOS] and the Ethics Committee of the clinical site). In contrast, VZU00022 was conducted in the U.S., with local IRB approval. It has been suggested to Vizuri that social norms in the Dominican Republic are such that they may markedly amplify the magnitude of the placebo response. If one assumes that the vehicle itself has no analgesic properties, then the placebo response in

VZU00023 (in the DR) was approximately twice what was seen in VZU00022 (in the U.S.).

This marked difference between the response to placebo (vehicle), using the same vehicle, in the U.S. study compared to the non-U.S. study, conducted in the Dominican Republic, appears to be consistent with the known higher rates of placebo response in studies conducted in Latin American countries[5], and which effect is within the well-known influence of cultural differences in placebo responses [6]. The differences between placebo responses in the same studies conducted in Latin America and Europe and the corresponding differences for active treatment response are tabulated below (Table 1–1). The data in Table 1 suggest that on average, the placebo response in a study conducted in a Latin American culture country (such as the Dominican Republic) will be circa 2.6 times greater than in the same study conducted in European countries. This, by extension, suggests that the placebo response in a Latin American study may be similarly higher compared to the same study conducted in the U.S., the U.S. culture being typically more European than Latin American. Per Figure 1–3 once daily application of vehicle reduced group mean OA pain score to 60% of baseline by Day 28 in the U.S. OTC study whereas the vehicle reduced group mean OA pain score to 25% of baseline by Day 33 in the Dominican Republic study. Looking at these percent of baseline values in a different light, the absolute reduction of OA pain score associated with vehicle treatment was 40% for the U.S. study and 75% for the Dominican Republic study. The “absolute reduction” is 100% less the percentage of baseline at the assessment time (i.e., the degree of pain relief associated with a treatment). So, the placebo (vehicle) effect in the Dominican Republic study appears to be 1.9-times greater than the vehicle effect in the U.S. study. This is well within the range of differences reported by Xu et al. (2016).[5]

Table 1–1. Differences in Latin American and European Placebo Responses and Corresponding Latin American and European Responses to Active Treatment (Source: Study VZU00023)

Study #	LA Placebo	EU Placebo	LA/EU		LA Active	EU Active	LA/EU
Study 1	61	28	2.18		38	45	0.84
Study 2	66	37	1.78		56	46	1.22
Study 3	58	35	1.66		51	55	0.93
Study 6	68	23	2.96		57	57	1.00
Study 9	42	13	3.23		60	52	1.15
Study 10	53	15	3.53		75	50	1.50
Average			2.56				1.11
S.D.			0.79				0.24
% SD			31%				21%

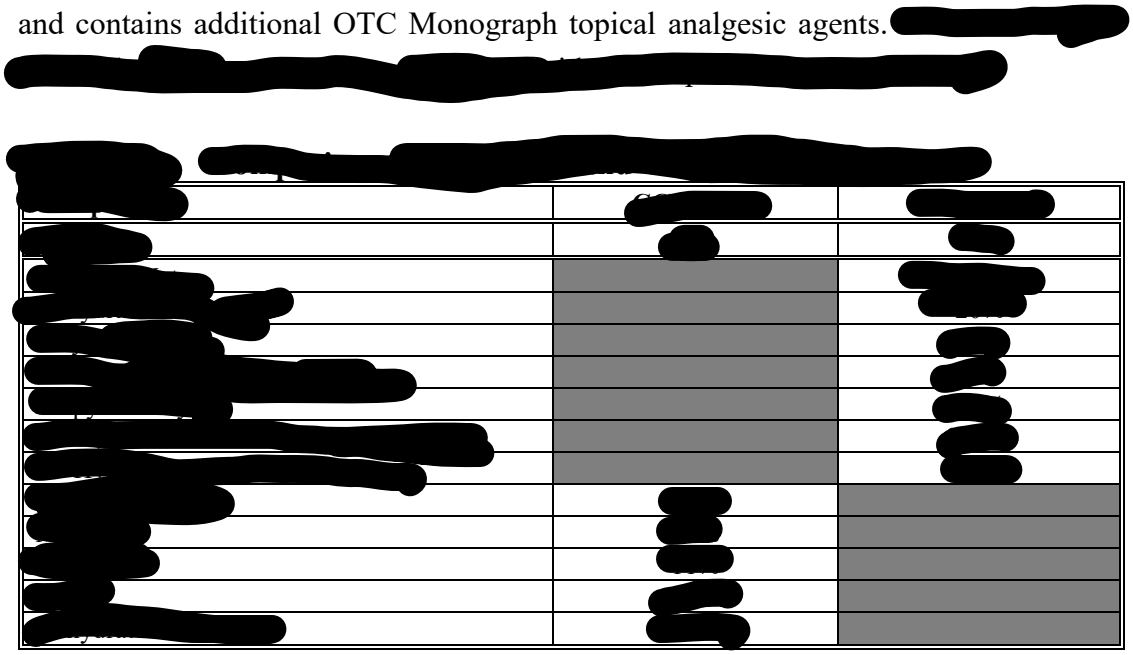
Data from Figure 1 in Xu *et al*., Arthritis Rheumatol., 68(suppl 10), Abstract # 2594 (2016)[5]

It can be seen, also, from Table 1–1 that the difference in active treatment response in Latin America conducted studies and European conducted studies is slight. One can speculate that the large differences noted for placebo responses and the small differences noted for active treatment responses may be due to a cultural difference in the expectations of Latin American subjects compared European subjects. The Latin American may tend to believe more strongly that what the doctor or clinic is doing will help them, ergo the high placebo responses in Latin America; whereas, the European subjects may have lower expectations of obtaining relief, and a lower placebo response as a result. For active treatment, if the study treatment is actually beneficial, then the responses of European subjects and Latin American subjects would be similar, as is reported by Xu *et al*. (2016).[5] The role of cultural differences in expectations regarding treatment outcomes is well recognized and has been addressed by Bhugra and Ventriglio (2015).[6]

In contrast to the magnitude of cultural effects on placebo response, the data presented by Xu et al. (2016) suggest that cultural differences in response to active treatment appear to be slight. [5] This suggests, in turn, that the pain relief efficacy data for active treatment (CGS-200-5) in study VZU00023 will hold up in the U.S. study planned under this protocol. Conversely, the large cultural differences in placebo responses, along with experience with vehicle response in a U.S. OTC product study, suggest that the vehicle response in the clinical study planned under this Investigational New Drug (IND) application will be much lower than was observed in study VZU00023 and likely similar to what was seen in the U. S. OTC product study.

1.2 NONCLINICAL TOXICOLOGY SUMMARY

Sponsor has conducted a number of non-clinical toxicology studies with high strength Capsaicin topical liquid. These studies have, for the most part, been conducted with a different formulation of high strength topical capsaicin than that which will be investigated under Protocol VZU00025. This alternate formulation is termed CGS-125 and contains additional OTC Monograph topical analgesic agents.



The CGS-125 formulation contains a number of OTC Monograph topical analgesics. These are known to have pharmacological activity and present the potential that the CGS-125 formulation could have more potential for toxicities than CGS-200, which contains none of these ingredients.

Both formulations contain similar levels of dehydrated alcohol (i.e., ethanol), so they are comparable in this regard, CGS-200 has, otherwise, only one compound that has known pharmacological activity (capsaicin) and it is at the same level as in CGS-125-5. The excipients in CGS-200 are all of low toxicity potential.

The non-clinical toxicity studies that have been conducted on CGS-125, which include one in which CGS-125 and CGS-200 were compared directly for tolerability on application to rats, are listed following with an outcome summary for each.

Central Nervous System (CNS) Safety Pharmacology

A Functional Observation Battery (FOB) Neurological Assessment in the Male Sprague Dawley Rat Following a Single Dermal Application (Study # 1015-2201 / CiTox Labs, Montreal, Canada)

CGS-125 (at 5%, 10% and 20% Capsaicin) tested at maximum practical dose. Single dermal application of 200 µL volume over 50 cm^2 area for 2 hrs then removal with PEG 300. No suggestion of neurological deficits or effects.

Respiratory Safety Pharmacology

A Respiratory Safety Pharmacology Study in Conscious Male Sprague Dawley Rat Following a Single Dermal Application (Study # 1015-2211 / CiTox Labs, Montreal, Canada)

CGS-125 (at 5%, 10% and 20% Capsaicin) tested at maximum practical dose. Single dermal application of 200 µL volume over 50 cm^2 area for 2 hrs then removal with PEG 300. No suggestion of respiratory deficits or effects.

Cardio-Vascular Safety Pharmacology

A Cardiovascular Function Safety Pharmacology Study in Conscious Telemetered Male Beagle Dog Following a Dermal Application (Study # 1015-2292 / CiTox Labs, Montreal, Canada)

CGS-125 (at 5%, 10% and 20% Capsaicin) tested at maximum practical dose. Single dermal application of 200 µL volume over 50 cm^2 area for 2 hrs then removal with PEG 300. No suggestion of cardio-vascular deficits or effects.

Tolerability on Application, Rabbit

Dermal Tolerance of Topical Capsaicin Formulations in Rabbits (Study # 2007-6987 / Charles River Laboratories, Horsham, PA)

CGS-125 (at 5% and 20% Capsaicin) tested at maximum practical dose. Single dermal application of 800 µL volume over 200 cm^2 area for 2 hrs then removal with PEG 300. Vehicle, 5% and 20% well tolerated. No suggestion of safety issues observed.

Tolerability on Application, Dog

A Single Dermal Application Pilot Tolerability Study in Beagle Dogs (Study # 2015-2182 / Charles River Laboratories, Horsham, PA)

CGS-125 (at 5%, 10% and 20% Capsaicin) tested at maximum practical dose. Single dermal application of 1600 µL volume over 400 cm^2 area for 2 hrs then removal with PEG 300. Vehicle, 5%, 10% and 20% well tolerated. No suggestion of safety issues observed.

Tolerability on Application, Rat

Single Dose Dermal Tolerance Study of Two Capsaicin Formulations (Study # 2007-3449 / Charles River Laboratories, Horsham, PA)

Capsaicin in CGS-125 (at 0% and 20% Capsaicin) and in CGS-200 (at 2%, 5% and 10% Capsaicin) tested at maximum practical dose.

Both formulation tested at maximum practical dose. Single dermal application of 200 µL volume over 50 cm^2 area for 2 hrs then removal with PEG 300.

CGS-125 Outcome: Vehicle and 20% well tolerated. No suggestion of safety issues observed.

CGS-200 Outcome: Both 2% and 5% well tolerated. 10% elicited strong aversion reaction in rats. No suggestion of safety issues. (Note: In non-U.S. clinical studies application of CGS-200-10% once daily for 1 hour on 4 consecutive days has been well tolerated.)

Repeat Dose Toxicology in Rats

A Seven Day Repeat Dose Dermal Toxicity Study of CGS-125 in Rats with a Four Week Recovery Period (Study # 2008-0727 / Charles River Laboratories, Horsham, PA)

CGS-125 (at 5%, 10% and 20% Capsaicin) tested at maximum practical dose. Seven (7) consecutive daily dermal applications of 200 µL volume over 50 cm^2 area for 2 hrs then removal with PEG 300. Vehicle, 5%, 10% and 20% well tolerated. No systemic or local toxicities elicited (on gross and histopathology examinations and assessments, hematology, urinalysis, or blood chemistries). No suggestion of safety issues.

Repeat Dose Toxicology in Rabbits

A Seven Day Repeat Dose Dermal Toxicity Study of CGS-125 in Rabbits with a Four Week Recovery Period (Study # 2008-0728 / Charles River Laboratories, Horsham, PA)

CGS-125 (at 5%, 10% and 20% Capsaicin) tested at maximum practical dose. Seven (7) consecutive daily dermal applications of 800 µL volume over 200 cm^2 area for 2 hrs then removal with PEG 300. Vehicle, 5%, 10% and 20% well tolerated. No systemic or local toxicities elicited (on gross and histopathology examinations and assessments, hematology, urinalysis, or blood chemistries). No suggestion of safety issues.

Mutagenicity

Bacterial Reverse Mutation Assay (Study # AE58RS.502-ICH.BTL / BioReliance, Rockville, MD)

Capsaicin in CGS-125 tested *in vitro* against *S. typhimurium* TA98, TA100, TA1535, TA1537; *E. coli* WP2 *uvr*A at up to 5000 µg/plate. No evidence of mutagenic activity.

Clastogenic Potential

In Vitro Mammalian Chromosomal Aberration Assay in CHO Cells (Study # AE58RS.331-CH.BTL / BioReliance, Rockville, MD)

Capsaicin in CGS-125 tested *in vitro* against Chinese Hamster Ovary cells (CHO) at up to 30 µg/mL No evidence of clastogenic activity

1.3 PREVIOUS CLINICAL EXPERIENCE

Study VZU00020

This was a clinical study comparing the single dose tolerability of 5% and 10% capsaicin in CGS-125 and in CGS-200 (VZU00020) demonstrated that CGS-200 with 5% and 10% capsaicin produced a mean burning- stinging pain ("BSP") score of not more than 2.5 on a 0 – 10 NRS scale. In this same study the number of subjects reporting an NRS BSP score of 5 or greater (on the 0 – 10 scale) is as tabulated in Table 1–3 below:

Table 1–3. Number of Subjects with BSP > 5 At Times After CGS-200-5 and CGS-200-10 Application in Study VZU00020

% Caps	15 Min Post	30 Min Post	60 Min Post	90 Min Post
5%	2/15	2/15	3/15	3/15
10%	3/15	1/15	3/15	2/15

Study VZU00021

This was a study in which CGS-125 formulation of 5% and 10% capsaicin and CGS-200 formulations of 5% and 10% were applied once daily for 1 hour on each of four sequential days to subjects with confirmed knee OA and a baseline NRS OA knee pain score of 5 or greater. OA knee pain was assessed daily on Days 1 (before the first application) and then on Days 2, 3 and 4 (prior to the daily application) and again on Days 5, 19 and 33. Burning-stinging pain at the application site was evaluated on a 0 – 10 NRS scale. Erythema, scaling and pruritus were also assessed and scored at each protocol assessment time.

In VZU00021, both CGS-200-05 and CGS-200-10 gave a high level of pain control with 85% or greater of subjects experiencing a reduction from baseline NRS of 50% or

greater and this pain relief lasted for at least 29 days after the last application of the investigational drug product. The degree and duration of pain relief was similar for CGS-125-05 but appeared to be less over the first 4 days for CGS-125-10:

Drug	**Criterion:** ≥ 50% NRS Reduction	**Day 1** 1st Appl.	**Day 2** 2nd Appl.	**Day 3** 3rd Appl.	**Day 4** 4th Appl.	**Day 5**	**Day 19**	**Day 33**
		Percent on Subject Knees Meeting the Criterion						
CGS-200-05		0%	42%	85%	88%	100%	81%	92%
CGS-200-10		0%	45%	97%	97%	100%	79%	86%
CGS-125-05		0%	60%	80%	80%	90%	100%	100%
CGS-125-10		0%	0%	57%	57%	100%	100%	100%

Both formulations at either strength were well tolerated and reduced OAKP by 75% or more compared to baseline. Analgesic effect persisted to Day 33 (last follow up day). No serious adverse events (SAEs), no adverse events (AEs) resulting in subject discontinuation or subject requested withdrawal, only AEs that were possibly, probably or definitely treatment related were: (a) local at the application site and Rheumatology Common Toxicity Criteria (RCTC) toxicity grades were generally 1 (mild) and at highest 2 (moderate) and were mostly BSP with less frequent erythema, pruritus, and scaling (latter only for CGS-125-10); and (b) coughing / sneezing during or following application (RCTC Grade 1, mild) which was observed in a higher proportion of CGS-125 subjects (40% - 60%) than in CGS-200 subjects (20% - 27%). Comparison of Day 33 (study exit) values for serum chemistry and hematology with values at screening showed no remarkable changes in any subjects and no differences for any subject, comparing Day 33 to Screening, that were atypical of the normal variations in serum chemistry and hematology values in individuals for blood sampling at different time points. In summary, no suggestion of systemic toxicities related to treatment was observed.

In Study VZU00021 neither vehicle or a true placebo was used as the study was designed to compare the CGS-200 formulation with the CGS-125 formulation in terms of tolerability and efficacy for a 4-day, once daily for 1-hour treatment regimen.

Study VZU00023

This was a vehicle-controlled study of safety, tolerability and efficacy of CGS-200 5% capsacian in subjects with OA of the knee. Single daily application for four consecutive days with 93 days (13 weeks) follow up.

CGS-200-5 was well tolerated and reduced OAKP at 13 weeks by 93% compared to baseline. No SAEs, no AEs resulting in subject discontinuation or subject requested withdrawal, only AEs that were possibly, probably or definitely treatment related were: (a) local at the application site and RCTC toxicity grades were generally 1 (mild) and at highest 2 (moderate) and were mostly BSP (in 100% of subjects) with less frequent erythema (72% of subjects), and pruritus (56% or subjects) ; and (b) coughing / sneezing during or following application (RCTC Grade 1, mild) which was observed in 20% of subjects. No suggestion of systemic toxicities related to treatment was observed.

In this study, Vehicle control had an unexpectedly high placebo effect, with reduction of OAKP scores by around 83% at 13 weeks. Unusually high placebo effects are known from the literature to occur in studies in Latin American countries such as the Dominican Republic.[5] No SAEs, no AEs resulting on subject discontinuation or subject requested withdrawal, only AEs that were possibly, probably or definitely treatment related were: (a) local at the application site and RCTC toxicity grades were generally 1 (mild) and at highest 2 (moderate) and were mostly BSP (in 35% of subjects) with less frequent erythema (15% of subjects), and pruritus (31% or subjects) ; and (b) coughing / sneezing during or following application (RCTC Grade 1, mild) which was observed in 3.8% of subjects. In this study, serum chemistries, hematology and urinalysis data were collected at screening but not at a later time point. However, as a reference point, no remarkable differences for serum chemistry and hematology were observed between screening values and vales at one month after study start in Study VZU00021. It was, therefore, concluded that in Study VZU00023 no remarkable differences in serum chemistry and hematology values between screening and one to three months after study start would be observed. No suggestion of systemic toxicities related to treatment was observed in Study VZU00023.

CGS-200 specific efficacy data from Study VZU00023 are summarized in the following figures:

Figure 1–1. Group Mean NRS Pain as Percent of Baseline

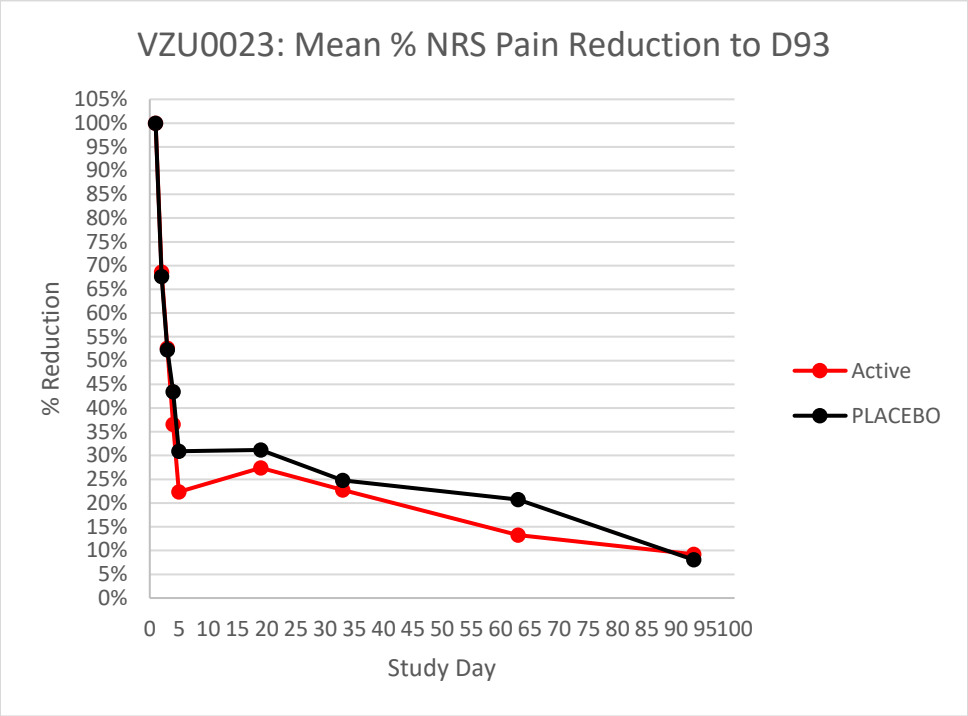
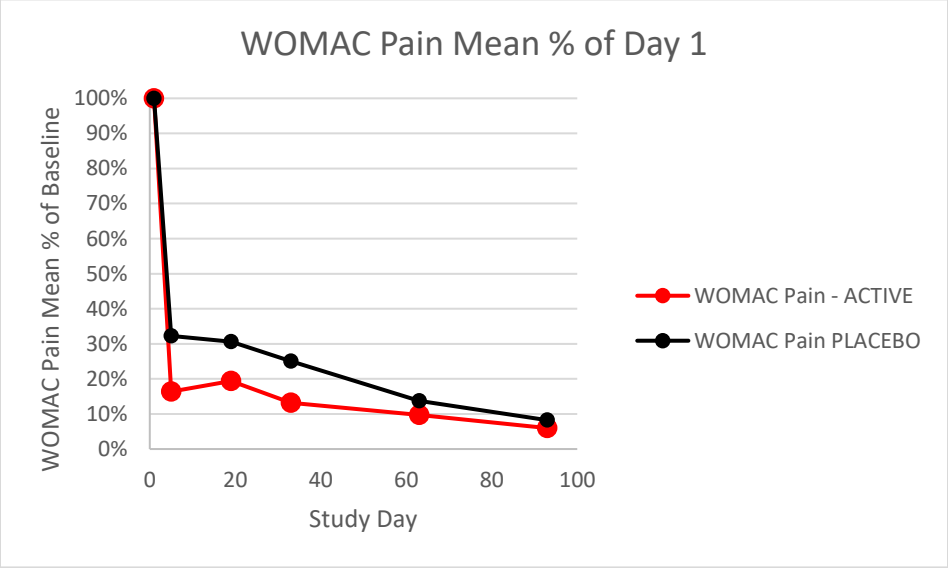
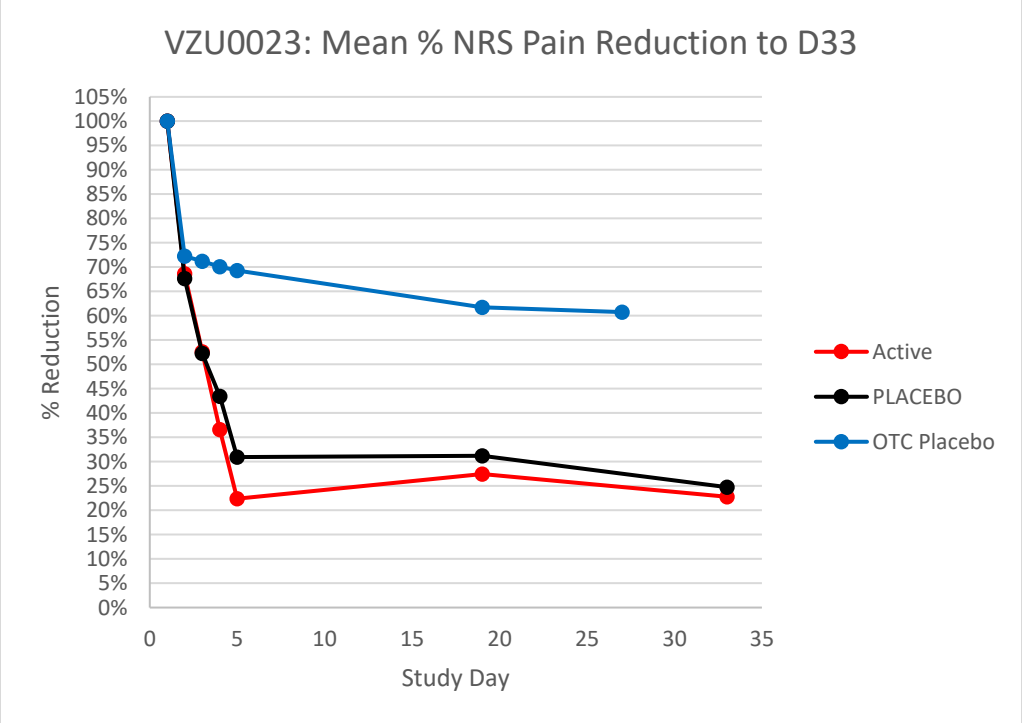


Figure 1–2. Group Mean WOMAC Pain as Percent of Baseline



It can be noted that for the NRS pain scores (Figure 1–1) the difference between placebo (vehicle) response and active treatment response is less than the difference between placebo (vehicle) response and active treatment response as assessed by the Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) pain subscale. Additionally, the placebo (vehicle) response is higher than expected based on data from a U.S. clinical study of Sponsor's OTC Tentative Final Monograph (TFM) capsaicin product (0.025% capsaicin topical liquid). The placebo response in that study was in the range of only a 60% reduction in OA knee pain scores relative to baseline (using a 100 mm VAS scale for pain assessment). This is illustrated in Figure 1–3, next page, which superimposes the U.S. vehicle response data onto the VZU00023 response data through Day 33. In the U.S. OTC study the final assessment time was at Day 28 and the vehicle was applied daily for 7 consecutive days either once daily or twice daily (with an application interval time of approximately 12 hrs). The vehicle response data shown in Figure 1–3 are for the once daily application of vehicle so as to be comparable to the once daily application of vehicle in study VZU00023. In the U.S. study, twice daily application of vehicle produced an approximately 55% reduction of group mean pain score relative to baseline.

Figure 1–3. U.S. Conducted OTC Study Vehicle (Placebo) Response Superimposed on Vehicle and CGS-200-5 responses in Dominican Republic Conducted Study VZU00023



This marked difference between the response to placebo (vehicle), using the same vehicle, in the U.S. study compared to the non-U.S. study, conducted in the Dominican Republic, appears to be consistent with the known higher rates of placebo response in studies conducted in Latin American countries [5], and which effect is within the well-known influence of cultural differences in placebo responses.[6] The differences between placebo responses in the same studies conducted in Latin America and Europe and the corresponding differences for active treatment response reported in Xu *et al*. (2016) suggest that on average, the placebo response in a study conducted in a Latin American culture country (such as the Dominican Republic) will be circa 2.6 times greater than in the same study conducted in European countries. [5] This, by extension, suggests that the placebo response in a Latin American study may be similarly higher compared to the same study conducted in the U.S., the U.S. culture being typically more European than Latin American. Per Figure 1–3 once daily application of vehicle reduced group mean OA pain score to 60% of baseline by Day 28 in the U.S. OTC study whereas the vehicle reduced group mean OA pain score to 25% of baseline by Day 33 in the Dominican Republic study. Looking at these percent of baseline values in a different light, the absolute reduction of OA pain score associated with vehicle treatment was 40% for the U.S. study and 75% for the Dominican Republic study. The "absolute reduction" is 100% less the percentage of baseline at the assessment time (i.e., the degree of pain relief associated with a treatment). So, the placebo (vehicle) effect in the Dominican Republic study appears to be 1.9-times greater than the vehicle effect in the U.S. study. This is well within the range of differences reported by Xu *et al*. (2016).[5]

1.4 SUMMARY OF SAFETY DATA

There have been three clinical trials conducted with CGS-200-5 and CGS-200-10 (VZU00020, VZU00021, and VZU00023). These have been conducted in the Dominican Republic with regulatory approval by CONABIOS and the local IRBs (Ethics Committees) for the study centers. With respect to the investigational drug product vehicle (CGS-200-0): One trial has been conducted in the Dominican Republic (VZU00023) and one trial was conducted in the U.S. (VZU00022). The U.S. study was for Sponsor's OTC TFM product that contains 0.25% capsaicin in CGS-200 vehicle. To date:

- No SAEs have occurred
- AE's that are possibly, probably or definitely associated with study treatment have been limited to mild-moderate and expected reactions at the site of application and which will resolve within a few days of occurrence.
- No suggestion of systemic toxicities has been observed

Hematology and serum chemistries were assessed for subjects in Study VZU00021 at screening and then again at Day 33 (last study assessment day and planned exit day). These are not tabulated here as for very study subject there were no remarkable changes or differences which were outside what is typical for hematology and serum chemistry assessments taken on the same person but at different times.

The amounts of capsaicin to be applied in this study and the likely systemic uptake of capsaicin by subjects in this study are quite small and further support that the topical applications of capsaicin to the subject's knees in the planned study will be safe for the subjects. For the initial investigation planned under this IND capsaicin will be applied in two strengths: 1% capsaicin (CGS-200-1) and 5% capsaicin (CGS-200-5). Also, the vehicle will be applied as a placebo control. The ingredients in CGS-200-1 and CGS-200-5 are as indicted in the tables that follow.

CGS-200 Formulations at 1% and 5% Capsaicin Content

Ingredient	CGS-200-5 % w/w	CGS-200-1 % w/w
Capsaicin	5	1
Dehydrated Alcohol	20	20
Polysorbate 80	10	8
Diethylene Glycol Methyl Ether	10	10
Propylene Glycol	10	10
Na Hyaluronate (~1,000K Daltons)	0.15	0.16
Na Hyaluronate SLMW (~20K Daltons)	0.30	0.32
Distilled Water	44.55	50.52
Totals	100.00	100.00

The amount of CGS-200 applied to the knee per application is an approximate maximum of 0.15 gram per knee. If two knees receive application, then the total amount of CGS-200 applied per application is approximately 0.30 gram and this is applied to an area of approximately 200 cm^2 (ca. 100 cm^2 per knee). Note that both knees will receive study drug application but only one knee will be the study knee on which

assessments are performed. Using CGS-200-5 as the maximum capsaicin strength product for investigations under this IND, the amounts of each component applied per application are provided in the table below.

Components Application Amounts for CGS-200 at 5% Capsaicin Content (knee(s) treated: 0.3 g CGS-200 Total)

Ingredient	CGS-200-5 % w/w	Per Application
Capsaicin	5	15 mg
Dehydrated Alcohol	20	60 mg
Polysorbate 80	10	30 mg
Diethylene Glycol Methyl Ether	10	30 mg
Propylene Glycol	10	30 mg
Na Hyaluronate (~1,000K Daltons)	0.15	0.45 mg
Na Hyaluronate SLMW (~20K Daltons)	0.30	0.90 mg
Distilled Water	44.55	133.65 mg
Totals	100.00	300.00 mg

These are all trivially small amounts for each of the components by the topical route.

For the capsaicin, the total maximum amount applied, 15 mg, would be a topical dosage of 0.21 mg/kg for a 70 kg person. As an application per cm^2 of surface area it would be 0.075 mg/cm^2.

One can compare the above 0.075 mg/cm^2 (75 $\mu g/cm^2$) with published data on capsaicin uptake from the 8% Qutenza patch (Babbar *et al*., 2009 [full copy in the Literature Appendix to Module 2]).[7] Babbar *et al*. (2009) report that areas of 1,000 cm^2 were treated with patches containing capsaicin at 640 µg capsaicin/cm^2. Treatment duration was generally for 60 minutes (same as intended for the protocol under this present IND) but in some cases, was for up to 90 minutes. The total amount of capsaicin applied and the unit dosage rate ($\mu g/cm^2$) reported by Babbar *et al*. (2009) and estimate for the initial clinical investigation planned under this IND and the ratio for comparing the Babbar et al. (2009) values to those estimated for the planned investigation are presented in the table below.

Dose Index	Babbar *et al*., 2009	Protocol VZU00025	**Ratio:** Babbar *et al*., 2009 / VZU00025
mg Total	640 mg	15 mg	43
$\mu g/cm^2$	640 $\mu g/cm^2$	75 $\mu g/cm^2$	8.5
mg/kg	9.1 mg/kg	0.21 mg/kg	43

Babbar *et al*. (2009) reported that the lower limit of quantification (LLOQ) for their serum capsaicin assay was 0.5 ng/mL, which can be considered a sensitive high-performance liquid chromatography (HPLC) method.[7] They also report that the percentage of subjects that had serum levels below the LLOQ was, in four different studies, respectively: 89%, 99%, 99.5%, and 94%. The median serum C_{max} for all subjects in all studies was reported to be *circa* 2 ng/mL with a time to maximum effect (T_{max}) of circa 1.5 hrs and with serum levels dropping to below LLOQ for all subjects by 4 – 5 hrs after patch removal.

Given that the unit surface area application rate for capsaicin in Protocol VZU00025 will be only about 12% of that used in the studies reported by Babbar *et al.*, (2009) it suggests that there would be no subjects in Protocol VZU00025 who would have capsaicin serum levels above an LLOQ of 0.5 ng/mL.[7]

In Non-Clinical studies (summarized above), no suggestions of potential systemic or site of application toxicities have been reported.

1.4.1 Possible Risks

All safety data obtained in this trial will be carefully evaluated and used to inform the design of any future clinical trials. The potential risks of study participation include those associated with exposure to capsaicin and possible allergic reactions to capsaicin or one of the other components of the investigational products. Effects of topical exposure to capsaicin include erythema, edema, papules, scaling, pruritus, stinging and burning pain. These manifestations may also occur in unintended locations through transfer of the investigational products from the treatment area to other sites on the skin, mucous membranes, and ocular surfaces. Inhalation of fumes or aerosolization of the investigational products may cause irritation of airways with symptoms such as coughing. A temporary rise in blood pressure (hypertension) or difficulty sleeping could occur if pain from stinging and burning is severe. All subjects will receive a full explanation of potential risks and will sign an informed consent form prior to study participation.

2.0 STUDY OBJECTIVES

The objectives of the present study are the following:

- To develop pain relief dose-response data for OAKP, compared to Vehicle, for the following concentrations of Capsaicin in CGS-200 vehicle: 1% and 5% using the WOMAC pain subscale (VAS formatted) as the primary pain index for relief of OAKP.
- To confirm, in a U.S. based population, the high safety profile for CGS-200-5 that was reported in Studies VZU00021 and VZU00023 in a Dominican Republic population.
- To develop data for relief of signs and symptoms of osteoarthritis using the WOMAC subscales for pain, stiffness and function and total WOMAC score.
- To develop OAKP relief data using the 100 mm VAS scale.

2.1 PRIMARY ENDPOINTS

The **Primary Efficacy** endpoint of this study will be to examine the extent of reduction in the WOMAC pain score, relative to baseline, provided by once daily, one-hour application of Vehicle (CGS-200-0), CGS-200-1 and CGS-200-5 at the following assessment times:

Baseline: $\leq$ 30 minutes prior to first daily application
Day 35 31 Days (+/- 3 days) after fourth daily application

and based thereon to determine whether the responses for treatment with CGS-200-0, CGS-200-1, and CGS-200-05 are significantly different from Vehicle and from each other at the primary endpoint time.

The **Primary Safety** Endpoints will be:

(1) The application of the study drug does not produce skin reactions (erythema, scaling, pruritus, or other) to a degree that is clinically of concern. Scoring of

erythema and scaling at the application sites and of pruritus will be assessed per the scoring systems in Appendix F.

(2) No SAE's either possibly, probably or definitely associated with study treatments.

(3) Safety labs (hematology, serum chemistry and urinalysis) do not produce other than minimal – mild toxicities (Grade 1 or Grade 2). Scoring of clinical, hematological and urinalysis out of range findings for toxicity grading will be per Appendix B.

2.2 SECONDARY ENDPOINTS

Secondary Efficacy endpoints will be:

(1) The extent of reduction in the WOMAC pain score, relative to baseline, provided by once daily, one-hour application of Vehicle (CGS-200-0), CGS-200-1, and CGS-200-5 at the following assessment times:

Baseline: ≤ 30 minutes prior to first daily application
Day 5 24 hrs (+/- 3) after last of the 4 daily applications
Day 19 15 days (+/- 3) after last of the 4 daily applications
Day 64 60 days (+/- 3) after the last of 4 daily applications
Day 94 90 days (+/- 3) after the last of 4 daily applications

(2) Day 5, 19, 35, 64, and 94 WOMAC scores on the stiffness and function subscales as well as total WOMAC score (including the WOMAC pain score).

Secondary Safety endpoints will be:

(1) The distribution by study arms of specific AEs (i.e.: local application site reactions), and other AEs (inclusive of findings for hematology, serum chemistry and urinalysis).

(2) Evaluate the amount of concomitant pain medications used overtime

Tolerability endpoints (which are secondary in nature) will be:

(1) The application of study drug does not produce burning-stinging pain ("BSP") at the application site to a degree that is not acceptable to the subject. BSP at the application site, this will be assessed using a 0 – 10 NRS scale without guideposts. "Acceptability" of BSP will be queried per subject at the end of each application period.

(2) The application of the study drug does not produce pruritus during application or in the 24 hrs post-application to a degree that is not acceptable to the subject or, if bothersome to the subject, cannot be managed by application of ice or a cold pack or compress.

3.0 STUDY DESIGN

3.1 OVERALL STUDY DESIGN

This is a multi-center, randomized, double-blind clinical trial to examine the comparative effects on OAKP of CGS-200-1 (1% Capsaicin content) (N=40), CGS-200-5 (5% Capsaicin content) (N=40), and CGS-200 Vehicle (no Capsaicin) (N=40) in subjects with OA of the knees according to the 1986 ACR criteria. Assigned doses will be applied at the clinic for 60 minutes on each of four consecutive days.

Subjects will be randomized to one of the three Arms in this study: CGS-200-1 or CGS-200-5 or CGS-200-0 (Vehicle). All subjects will receive 4 consecutive days of treatment and will then be followed up until the Day 94 visit.

Subjects will receive the study arm appropriate treatment as a topical application over the frontal aspect of the knee(s) once daily on four consecutive days. The applications will be at the clinic but by the subject wearing gloves under supervision of clinic personnel. The application will be left in place for 60 minutes and then washed off at the clinic by clinic personnel. The amount of Investigational Drug Product to be applied is estimated to be approximately 0.13 mL based on experience in prior studies. Even though both knee(s) will receive application of study test materials, with regard to reduction in WOMAC pain and VAS pain score associated with study treatments, only one knee will be indicated as the "Study Knee". This will be the knee with the highest WOMAC pain score at baseline. If both knees have equal WOMAC pain scores at baseline, then the right knee will be considered the "Study Knee" with regard to WOMAC pain and VAS pain score reduction.

Data will be collected from Day 1 through Day 5 and then again on Days 19, 35, 64, and 94 for efficacy, tolerability, and safety measures. The Investigators, all site staff and Clinical Research Organization (CRO) personnel (except the Medical Monitor providing safety oversight) directly involved in the study will remain blinded to the treatment assignment throughout the trial.

3.2 DOSE LIMITING TOXICITY

AEs and SAEs will be assessed according to the Rheumatology Common Toxicity Criteria (RCTC) v2.0[8] (Appendix B).

Dose limiting toxicity (DLT) stopping rules for the study drug are based mainly on Grade 2 events related to the study drug, with the following exceptions:

1. Cutaneous CGS-200-1 (Capsaicin 1% Topical Liquid) and CGS-200-5 (Capsaicin 5% Topical Liquid) have the potential for being associated with Grade 2 administration site reactions such as erythema, pain and edema, and the DLT threshold has been set at Grade 3.

2. The cut-point of Grade 3 to define a DLT and stop further administration of study drug was selected for the safety of subjects since the RCTC only require permanent discontinuation of drugs that attain a Grade 4.

A DLT will be defined as any toxicity occurring within 14 days of treatment with the investigational product, and meeting the following criteria:

- ≥ Grade 3 AE including:
  - Allergic / Immunologic: immune reactions, rhinitis;
  - Cardiac: hypertension, hypotension;
  - Dermatologic: reaction at site of study drug administration;
  - Neuropsychiatric: inability to concentrate, insomnia (in absence of pain), peripheral sensory neuropathy.
- Any other ≥ Grade 2 AE (excluding AEs captured above and pre-existing OA-related conditions).

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 INCLUSION/ EXCLUSION CRITERIA:

Subjects entering the study must meet all inclusion and exclusion criteria.

4.1.1 Inclusion Criteria:

The subject must meet all of the following:

1. Able to comprehend the informed consent form (ICF) and provide Informed Consent, and capable of complying with all study procedures;
2. Male or female, 35 years of age to 75 years;
3. OA of the at least one knee according to 1986 ACR Classification Criteria;
4. OA of at least one knee must be confirmed by tibiofemoral joint radiographs obtained within the past 6 months;
5. RF negative and ESR <40 mm/hr;
6. Chronic knee pain in at least one knee for $\geq$ 3 months;
7. WOMAC pain score of $\geq$ 250 (using VAS WOMAC format) at screening, and at baseline, in at least one knee;
8. Knee pain score of $\geq$ 5 on the NRS pain scale at screening, and at baseline, in at least one knee;
9. Knee pain is not potentially due to acute trauma unrelated to OA (no acute traumatic knee injury in medical history);
10. No burning-stinging pain, unrelated to subject's knee pain, at intended site of application;
11. Knee pain must be greater than pain in any other part of subject's body;
12. ACR global functional status I, II, or III (excluding IV);

13. If female, subject must be past childbearing age or otherwise must test negative for pregnancy. Males and females must agree to use effective birth control for at least 30 days after last dose of study drug.

4.1.2 Exclusion Criteria:

The subject must not have any of the following:

1. Spontaneously improving or rapidly deteriorating OA of the knee;

2. Rheumatoid or psoriatic arthritis, or a form of arthritis (e.g. gout, pseudogout), Paget's disease of bone, or any other disease affecting the joints that are inconsistent with a diagnosis of idiopathic OA;

3. Use of topical, oral, or injectable steroids for 1 month prior to screening, or intraarticular-visco-supplementation within 3 months prior to screening;

4. Used any capsaicin-containing product on or in the vicinity of the knee within 4 weeks prior to screening;

5. Used topically applied products (including emollients or moisturizers) on or in the vicinity of the knees or shaved the knees within 2 days prior to the first application of study drug; or an open wound near the knee; cutaneous erythema or edema; any inflammatory skin lesions such as eczema or psoriasis; cutaneous infections; or any other compromise of the skin;

6. A history of sensitivity to topical substances inclusive of OTC topical analgesics;

7. Significant cardiovascular, renal, or other diseases or conditions, or laboratory or other test abnormalities that, in the opinion of the Investigator, would contraindicate participation in the trial;

8. Labile or poorly controlled hypertension;

9. A psychiatric disorder or significant anxiety or depression that could interfere with the subject's compliance with study procedures or completion of the study;

10. Requires daytime use of medications or substances (alcohol, benzodiazepines, barbiturates, muscle relaxants, tranquilizers, hypnotics) that could diminish their cognitive ability to comply with study procedures;

11. A history of drug or alcohol abuse within one year prior to screening;

12. Requires or anticipates any surgical procedure within 3 months prior to screening, has had surgery on the affected joint within 6 months prior to screening, has a prosthesis in either knee, or would require surgery while participating in the trial;

13. Pregnant or nursing;

14. Treated with an investigational drug, device or therapy within 30 days prior to screening.

15. Body mass index greater than 45 kg/m^2

16. Skin on or near knee is broken or damaged or if there is an open wound on or near the knee.

4.2 REPLACEMENT OF SUBJECTS

Subjects that do not receive 4 complete consecutive daily doses and/or drop out before completing the Day 35 visit may be replaced if the reason for dropping out is other than lack of drug product tolerability. A dose will be considered complete when at least 80% has been delivered on any study drug administration day; dosing will be considered complete overall when a total of at least 80%, in the aggregate, has been delivered across all study treatment days. Subjects that drop out or who cannot be followed up from after the Day 5 visit until the Day 35 visit may be replaced. Up to 10 subjects per arm may be replaced.

5.0 STUDY TREATMENT

5.1 CGS-200-1, CGS-200-5, AND CGS-200-0 (VEHICLE)

5.1.1 Formulation

CGS-200-1 and CGS-200-5 are topical analgesic liquids intended for application to intact, non-irritated skin in adults with musculoskeletal pain, including pain of OA of the hands, wrists, elbows, or knees for the relief of pain, reduction of stiffness, and increased functional activity.

CGS-200-1 is a multi-component formulation in which the active ingredient for the intended therapeutic effect is capsaicin at a level of 1% for this study.

CGS-200-5 is a multi-component formulation in which the active ingredient for the intended therapeutic effect is capsaicin at a level of up to 5% for this study.

CGS-200-0 (Vehicle) contains all of the ingredients in CGS-200-1 and CGS-200-5 except for capsaicin.

The composition of study test materials is provided in the table below.

Ingredient	CGS-200-5 % w/w	CGS-200-1 % w/w	CGS-200-0 Vehicle % w/w
Capsaicin	5	1	0
Dehydrated Alcohol	20	20	22.5
Polysorbate 80	10	8	7
Diethylene Glycol Methyl Ether	10	10	10
Propylene Glycol	10	10	10
Na Hyaluronate (~1,000K Daltons)	0.15	0.16	0.17
Na Hyaluronate SLMW (~20K Daltons)	0.30	0.32	0.33
Distilled Water	44.55	50.52	50
Totals	100.00	100.00	100.00

CGS-200-1, CGS-200-5, and CGS-200-0 Vehicle will be stored at room temperature (15 - 30°C) in a limited access location, protected from excessive light and heat. Storage conditions must also comply with the site's institutional procedures and all applicable regulatory requirements.

Under clinic supervisions, each dose will be applied by the subject (who will be wearing gloves provided by the clinic) to the knee(s) over a 10 x 10 cm area on Days 1, 2, 3, and 4 and at each application, will be washed off by clinic personnel after 60 minutes (± 5 min).

5.1.2 Packaging, Labeling and Storage

The vial label will contain the following information at a minimum:

- Blinded code number
- Volume (single dose vial; fill volume is up to 0.35mL)
- Storage instructions
- Manufacture Date
- Investigational drug statement
- Name of manufacturer
- Name of sponsor

Study drug inventory/accountability forms will be monitored during the study and reconciled by the study monitor at the end of the study. All used and unused investigational study drug must be accounted for on a study drug accountability form provided to the investigator by the site monitor.

5.1.3 Rationale for Dose Selection

In a previous clinical investigation with CGS-200 5% and 10% capsaicin (Study VZU00021), both strengths gave essentially the same degree of pain relief and over essentially the same time course to maximum effect and lasting at least 29 days after cessation of treatment. Both strengths were well tolerated. Based on this, the choice of CGS-200-05 as the high dose Arm in this study is seen as rational. For the low dose Arm, CGS-200-1 was selected on the basis of being a reduction of 5-fold from the 5% dose, which degree of reduction is likely to give a lower response than the 5% dose based on modeling of analgesic responses from 7 days of QD and BID doses

of 0.25% capsaicin in CGS-200 observed in a clinical study of Sponsor's marketed OTC Monograph capsaicin topical product.

5.1.4 Dosage and Administration

The study medication is for external use only and will be administered at the clinic by the subject under the supervision of trained site personnel. Wearing gloves, supplied by the clinic staff, a single dose of the assigned treatment will be topically applied to each knee on each of four dosing days. Both knees will be treated for all subjects, if possible, however only one knee will be the study knee on which assessments are performed. The first application of medication will be at Visit 2 on Day 1 (initiated at Time 0). Dosing on each of the three subsequent treatment days should be performed at the same time of day ±2 hours in relation to the start time of the initial dose on Day 1.

With the knee relaxed, in a straight and horizontal position, treatment will begin by identifying a 10 cm by 10 cm area where the upper boundary is 1 cm above the patella, the center is aligned with the midline of the patella, and the line bisecting the 10 cm by 10 cm square has 5 cm on either side medially and laterally to the midline of the patella. Each application of the study medication will consist of a single pass of the roller ball over the knee so as to completely cover the designated treatment area. The treatment will be applied continuously beginning at the upper left corner of the square and moving the rollerball horizontally to the upper right corner and moving back and forth in a continuous pattern in a downward progression until the entire square is covered. This should result in moistening the skin providing a thin film of medication (approximately 0.13 mL [or 0.13 gram] of drug product applied to 100 cm^2 of knee surface, which represents 1.3 mg of solution per cm^2). Areas that were already moistened should not be recoated. The study medication should not be applied to a knee if the subject is still experiencing stinging, burning, pruritus, erythema, or scaling from a prior application to that knee. In the case of a dose that is skipped, the subject should return as scheduled for their next visit at which time they may receive the next scheduled application of study medication if their symptoms have subsided. The treatment period will not be extended beyond 4 days.

During the application process, care must be taken not to contaminate the outside of the bottle, other body surfaces, or equipment or other surfaces in the room. Any suspected contamination should be dealt with by washing off the formulation as soon as possible.

The subject's knees will remain uncovered for 60 minutes (up to 65 minutes) after dosing to allow for assessments and proper absorption of the study medication. The subject must avoid touching the knee area during this time. The knees will then be cleansed by trained personnel according to specific procedures designed to remove any remaining residual formulation from the surface of the skin. After the area is cleansed, the subject may cover their knees, but should avoid doing so if possible. It is recommended that the subject wear shorts or a skirt during the treatment period rather than long pants. During the four days of treatment, subjects should also avoid exposing the knees to any form of heat (hot water, vigorous exercise, direct sunlight, etc.). If a subject experiences intolerable pain or severe irritation from the study medication, they may apply cold water, ice, or a cold pack or cold compress to their knee. If the subject continues to have unbearable pain, they should contact the study site for help with pain management. In the event of an allergic reaction or medical emergency, the Medical Monitor must be contacted immediately.

Treatment assignment for all subjects enrolled in this study will be double-blind; the subjects and all site personnel and CRO personnel (except for the medical monitor providing safety oversight) involved in this study will not know the treatment given to any subject. Every effort should be made to maintain the study blind.

Subjects will be monitored closely during and after application of treatment for any signs of acute adverse reactions. If an allergic reaction occurs, suggested guidelines are as follows:

- Grade 3 or higher adverse reaction:
  - If treatment is ongoing, it must be immediately and permanently discontinued, the study drug should be washed off, and the subject should be treated symptomatically as clinically indicated.
  - The subject will be followed for safety as clinically indicated until the toxicity resolves, and in the opinion of the investigator, no further follow-up regarding the toxicity is needed. Complete documentation of the event is required.

- Grade 2 adverse reaction:
  - If treatment is ongoing, it must be immediately interrupted and the subject should be treated symptomatically as clinically indicated.
  - Once the subject has recovered to baseline and, if in the opinion of the investigator the benefit/risk is favorable, consideration can be given to restarting the treatment the next day after pre-medicating with an H2-receptor antagonist and acetaminophen.
- Grade 1 adverse reaction:
  - If treatment is ongoing, it may continue, but the subject should continue to be monitored carefully to ensure that ongoing signs and symptoms do not progress and worsen warranting intervention as described above.

5.1.5 Reporting Product Defects

Any defects with the investigational products must be reported *immediately* by the site to the Medical Monitor and Vizuri Health Sciences with further notification to the site monitor.

5.2 CONCURRENT MEDICATIONS

5.2.1 Allowed Regimens

Subjects may continue their baseline medication(s) as long as the medications are not prohibited as outlined in Section 5.2.2. If for any reason deemed necessary by the investigator, a subject requires additional medication(s) or change of dose, the medication(s), dosage change, route of administration, start and stop dates, and the indication for which it was given must be recorded in the source documents and electronic case report form (eCRF).

5.2.2 Prohibited Medications

Subjects should not receive any of the following medications through Day 94 and for the additional times specified below:

- Topical, oral or injectable steroids for 1 month prior to screening, or intra-articular-visco-supplementation within 3 months prior to screening;
- Any capsaicin-containing product on or in the vicinity of the knee within 4 weeks prior to screening;
- Topically applied products (including emollients or moisturizers) on or in the vicinity of the knees within 2 days prior to the first application of study drug;
- Topical or any other therapy on the knees that, in the Investigator's opinion, might affect the study evaluation of signs/symptoms;
- Daytime use of medications or substances (alcohol, benzodiazepines, barbiturates, muscle relaxants, tranquilizers, hypnotics) that could diminish cognitive ability to comply with study procedures;
- Investigational drug, device or therapy within 30 days prior to screening.

5.3 PROHIBITED PROCEDURES

Subjects should not undergo any of the following procedures through Day 94 and for the additional times specified below:

- Anticipates any surgical procedure within 3 months of screening;
- Had surgery on the affected joint within 6 months prior to screening;
- Prosthesis at the index joint.
- Subjects should not shave their knees within 2 days before Day 1 and through Day 5.

6.0 STUDY PROCEDURES

6.1 SCREENING VISIT

Written informed consent must be obtained before any screening procedures are performed that are not considered part of normal patient care. Screening for many subjects will be completed in 2 visits. During the first visit, all screening activities with the exception of obtaining laboratory work should be completed. Prior to this second visit in which laboratory work will be collected, subjects must begin fasting (except water) for chemistry assessment beginning at midnight prior to the blood draw visit. If a subject presents for the first screening visit and has fasted on his/her own since midnight the blood draw may be taken at the first screening visit and a second screening visit will not be required. Table 6–1 shows all the procedures to be conducted at the Screening Visit. Subjects should plan to be in the clinic a minimum 1.5 hours (up to 2 to 3 hours) each visit.

Table 6–1 Screening Procedures

Assessment	Within 28 days of Study Day 1
Clinic Visit	X
Informed Consent	X
Inclusion / Exclusion	X
Demographics	X
Medical & Medication History	X
Physical Exam	X
Heights & Weight	X
Vital Signs[a]	X
Knee X-rays[b]	X
12-lead electrocardiogram (ECG)[c]	X
Clinical Laboratory Tests[d]	X
Serum Pregnancy or Follicle-stimulating hormone (FSH) Test[e]	X
Application Site Pain, Erythema, Edema, Scaling, Pruritus Assessment[f]	X
Exploratory Assessment of OA Knee Pain[g]	X
WOMAC	X
Assessment of Concomitant Medications[h]	X

[a] Vital signs include temperature, blood pressure, heart rate and respiratory rate.

[b] Knee-X-rays of both knees must be obtained unless films/images performed within 6 months before screening. Copies of film and results will be requested.

[c] Standalone 12-lead ECG.

[d] Clinical Laboratory Tests (Appendix A):
Hematology: complete blood count (CBC) including red blood cells (RBC), hemoglobin, hematocrit, MCV, MCH, MCHC, white blood cells (WBC), differential white cell count, platelet count.
ESR
Chemistry: Blood Urea Nitrogen (BUN), creatinine, uric acid, bilirubin (total), sodium, potassium, calcium, magnesium, phosphorous (inorganic), chloride, bicarbonate, alkaline phosphatase (ALK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), creatine phosphokinase (CPK), albumin, total protein, and glucose
Immunoglobulin M (IgM) RF
Urinalysis: pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, specific gravity, leucocytes. Clinically significant abnormal dipstick results will require microscopic analysis.

[e] Serum pregnancy test for premenopausal women; FSH test to confirm postmenopausal status (females only) for up to 2 years after cessation of menses
[f] Application site pain will be assessed on the NRS (0-10); application site erythema/edema will be assessed using modified categorical Draize test (0-3).[9] Scaling and pruritus will also be scored on a similar categorical scale (0-3). Scoring for application site pain (not related to knee pain) and for erythema, edema, scaling and pruritus. (Appendix F and G).
[g] Exploratory assessment of OA knee pain (average daily pain and daily worst pain) (Appendix F).
[h] Document all medications taken within 90 days of the Screening visit.

6.2 ON-TREATMENT EVALUATIONS:

Table 6–2 shows all procedures to be conducted during Study Days 1 to 4 when study drug is applied in the Clinic.

Table 6–2 On Treatment Evaluations

Assessment	Treatment Days			
TIMEFRAME	1	2	3	4
Clinic Visit	X	X	X	X
Randomization	X			
Vital Signs[a]	X	X	X	X
Urine Pregnancy Test[b]	X			
Application Site Pain, Erythema, Edema, Scaling, Pruritus Assessment[c]	X	X	X	X
VAS OA Knee Pain Assessment[d]	X	X	X	X
WOMAC[e]	X			
Exploratory Assessment of OA Knee Pain[f]	X			
Drug Administration	X	X	X	X
Assessment of Concomitant Medications	X	X	X	X
AE Assessments	X	X	X	X

[a] Vital signs include temperature, blood pressure, heart rate and respiratory rate pre-dose on Days 1-4 and at 90 minutes (± 5 min) after applying study drug to knees.
[b] Urine pregnancy test at baseline on Day 1 for premenopausal women.
[c] Application site pain will be assessed on NRS (0-10); application site erythema/edema will be assessed using modified categorical Draize test (0-3). Scaling and pruritus will also be scored on a similar categorical scale (0-3). Scoring for application site pain (not related to knee pain) will be performed on drug administration Days 1-4 (pre-application [≤30 min], and at 15 (± 5 min), 30 (± 5 min), 60 (± 5 min) and 90 minutes (± 5 min) after application) and on Days 5, 20, and 35. Application site skin reactions (erythema, edema, scaling, pruritus) will be assessed on drug administration Days 1-4 (pre-application [≤ 30 min], and at 15 (± 5 min), 30 (± 5 min), 60 (± 5 min) and 90 minutes (± 5 min) after application). (Appendix E and Appendix F).
[d] OA knee pain to be scored on 100mm VAS scale pre-treatment (≤ 30 min) on Days 1-4.
[e] WOMAC Pain, Stiffness, and Physical Function will be performed on Day 1 prior to drug administration (≤ 30 min).
[f] Exploratory assessment of OA knee pain (average daily pain and daily worst pain) (pre-application [≤30 min]) (Appendix F).

"BASELINE" is defined in this study as the WOMAC scores (pain, stiffness, function) and the VAS OA knee pain score recorded within 30 minutes of the first application of study drug.

6.3 FOLLOW-UP PERIOD EVALUATIONS

Table 6–3 shows all procedures to be conducted during the Follow-up Period (Clinic Days 5, 19, 35, 64 and 94).

Table 6–3 Follow-up Period Evaluations

Assessment	Follow-up Period Days					
TIMEFRAME	5 (24hrs post Day 4 [±4 hrs])	19±3 (Post-Treat Wk 3)	35±3 (Post-Treat Wk 5)	64 (± 3), (Post-Treat Wk 9)	94 (± 3) (Post-Treat Wk 13)	Unscheduled, Early Termination, SAE[e]
Clinic Visit	X	X	X	X	X	X
Vital Signs[a]	X				X	X
Physical Exam						X
Clinical Laboratory Tests	X		X		X	X
Application Site Pain, Erythema, Edema, Scaling, Pruritus Assessment[b]	X	X	X	X	X	X
VAS OA Knee Pain[c]	X	X	X	X	X	X
WOMAC[d]	X	X	X	X	X	X
Assessment of Concomitant Medications	X	X	X	X	X	X
AE Assessments	X	X	X	X	X	X
Study Exit					X	

[a] Vital signs include temperature, blood pressure, heart rate and respiratory rate.

[b] Application site pain will be assessed on NRS (0-10); application site erythema/edema will be assessed using modified categorical Draize test (0-3). Scaling and pruritus will also be scored on a similar categorical scale (0-3). Scoring for application site pain (not related to knee pain) will be performed on Days 5 (24 hrs [+/- 4 hrs]), 19 (+/- 3 days), 35 (+/- 3 days), 64 (+/- 3 days) and 94 (+/- 3 days). Application site skin reactions (erythema, edema, scaling, pruritus) will be assessed on Days 5 (24 hrs [+/- 4 hrs]), 19 (+/- 3 days), 35 (+/- 3 days), 64 (+/- 3 days) and 94 (+/- 3 days). (Appendix E and Appendix F).

[c] VAS OA knee pain will be performed on Days 5 (24 hrs [+/- 4 hrs]), 19 (+/- 3 days), 35 (+/- 3 days), 64 (+/- 3 days) and 94 (+/- 3 days).

[d] WOMAC Pain, Stiffness, and Physical Function will be performed on Days 5 (24 hrs [+/- 4 hrs]), 19 (+/- 3 days), 35 (+/- 3 days), 64 (+/- 3 days) and 94 (+/- 3 days).

[e] Refer to Section 6.5 for assessments to be completed at time of SAE, early termination or unscheduled visit.

6.4 BIRTH CONTROL REQUIREMENTS

Female subjects of childbearing potential must agree to use a highly effective method of birth control **(defined as those, alone or in combination, which result in a low failure rate, i.e., less than 1 percent per year, when used consistently and correctly)** for at least 30 days after last dose of study drug.

Male subjects must agree to use a highly effective method of birth control **(defined as those, alone or in combination, which result in a low failure rate, i.e., less than 1 percent per year, when used consistently and correctly)** for at least 30 days after last dose of study drug.

The acceptable methods of birth control are:

- Implanted, injected, or oral contraceptives
- Intrauterine devices
- Barrier methods (male condom, female condom, diaphragm)
- Sexual abstinence (when this is the preferred and usual lifestyle of the subject)
- Male subjects who have had a vasectomy
- Female subjects who have had a hysterectomy, tubal ligation, or bilateral salpingectomy or women of postmenopausal status

In addition, male subjects must not donate sperm during the study and for 30 days after the last dose of study drug.

6.5 ASSESSMENTS AT TIME OF SAE, EARLY TERMINATION OR UNSCHEDULED VISIT

Additional activities may be performed at the Investigator's discretion at the onset of an SAE, when subjects are prematurely taken off study, and/or for an unscheduled visit.

- Assess vital signs (BP, HR, RR, and T)
- Perform abbreviated symptom-driven physical exam (PE)
- Application site pain will be assessed on numerical pain rating scale (0-10); application site edema will be assessed using categorical Draize test (0-3). Scoring for application site pain (not related to knee pain) and for erythema and edema will be performed at Early Termination and at Unscheduled Visits.
- VAS OA knee pain and WOMAC will be performed at Early Termination and at Unscheduled Visits.
- Collect blood:

  For local laboratory analysis:

- CBC with automated differential and platelets, and serum chemistry

- Document AEs and concomitant medications

6.6 STUDY BLOOD DRAW VOLUME

The total blood volume to be collected during the study is approximately 60 ml (two ounces).

6.7 RECOMMENDATIONS FOR MANAGEMENT OF POTENTIAL TOXICITIES

6.7.1 Allergic Reaction, Burning, or Pruritus

In the case of any life-threatening event occurring during the treatment, the study drug must be immediately and permanently discontinued. While corticosteroids are strongly discouraged, they may be used if they are necessary for the safety of the subject.

- **Rash/pruritus/urticaria**

  - If subject develops rash, pruritus, or urticaria, interrupt treatment if it is ongoing and promptly assess subject for any other associated signs/symptoms (e.g., hypotension, fever, respiratory distress).

    - Consider treating with H2 receptor antagonists as clinically indicated. If rash / pruritus / urticaria is isolated and resolves either spontaneously or with intervention, treatment with the study drug may be restarted.

6.8 CONCOMITANT MEDICATIONS/RESCUE MEDICATIONS

Subjects may continue their baseline medication(s) as long as the medications are not among the prohibited medications listed in Section 5.2.2. The daily dose of each medication should be maintained throughout the study since any changes to this background regimen may have an effect on the assessment. Subjects are allowed to increase dosage of NSAIDs or use analgesics to treat minor pain throughout the study, provided all concomitant medications are back to baseline dosages within 24 hours of a clinical assessment visit.

If for any reason deemed necessary by the investigator, such as in the event of a substantial disease flare which cannot be treated with increased drugs (NSAIDs) or narcotic, a rescue medication can be initiated at any time that is in the best interests of the subject. Rescue medication should be carefully considered by the principal investigator (PI) since there may be an effect on the results of the study. All changes and start and stop dates, and the indication for which it was given must be recorded in the source documents and eCRF. Routine changes (dose, route, etc.) to the background treatments should not be performed.

6.9 STOPPING CRITERIA

6.9.1 Criteria for Adverse Event Assessment

All AEs will be graded according to the RCTC v.2.0 (Appendix B). Please refer to Section 8.0, Safety Assessments for additional information.

6.9.2 General Criteria for Stopping Study Drug

The study drug will be permanently discontinued for any subject who meets a DLT criterion as outlined in Section 3.2.

6.9.3 Stopping Criteria

Any ≥ Grade 3 event considered related to the study drug and occurring during administration of the study drug will result in its permanent discontinuation for that subject. The Medical Monitor should be notified immediately and the subject should be followed for safety as clinically indicated until the toxicity resolves and in the opinion of the investigator, no further follow-up regarding the toxicity is needed.

6.10 WITHDRAWAL OF SUBJECTS FROM STUDY

Subjects will be free to withdraw from treatment or from the study at any time for any reason, or they may be withdrawn/removed, if necessary (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Subjects will be removed from treatment for the following reasons:

- Unacceptable acute toxicities defined as:
  - Occurrence of a DLT

Subjects will be removed from the study for the following reasons:

- Withdrawal of consent
- Non-compliance/Lost to follow-up
- Pregnancy

If treatment with study drug is interrupted and permanently stopped, subjects should remain on study and will be followed for scheduled safety and study assessments through Day 35. If the subject goes onto other treatment, this should be noted in the source documents and the concomitant medications eCRF.

7.0 CLINICAL ACTIVITY

Evidence of clinical activity will be assessed by the VAS OA knee pain scores recorded at pre-dose (≤ 30 min) on Days 1 2, 3, 4, and on Days 5, 19, 35, 64, and 94.

The WOMAC instrument will we be used to evaluate the effectiveness of CGS-200-1 and CGS-200-5 in the management of signs and symptoms of OA of the knee in addition to just management of OA knee pain on Days 5, 19, 35, 64, and 94.

8.0 SAFETY ASSESSMENTS

8.1 ADVERSE EVENTS

8.1.1 Definitions

The AE monitoring period begins with the start of study drug administration on Day 1 and continues through Day 94.

ADVERSE EVENT EXPERIENCE (AE) – any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of an investigational drug but is not necessarily caused by the investigational drug. This includes worsening (e.g.; increase in frequency or severity) of pre-existing conditions.

SERIOUS ADVERSE EVENT (SAE) – an AE resulting in any of the following outcomes:

- Death
- Life-threatening (**immediate** risk of death)
- Inpatient hospitalization
- Prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Medically important*

*Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in a subject's hospitalization, or the development of drug dependency or drug abuse.

UNEXPECTED ADVERSE EVENT – any adverse event, the specificity or severity of which is not consistent with the current Investigator Brochure (IB). Expected means that the event has previously been observed with the study drug and is identified and/or

described in the current IB. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.

8.1.2 Reporting to the Sponsor

All AEs that are identified from the start of study drug administration and through Day 94 will be documented in the source documents and the AE eCRF. All data fields on the AE eCRF should be completed.

SAE must also be documented on the SAE Worksheet and sent to the sponsor/designee within 24 hours of site personnel becoming aware of an SAE. The SAE Worksheet should be completed as much as possible but should not be held until all information is available. Additional information, follow-up information, and corrections should be provided on subsequent SAE Worksheets that are clearly identified as follow-up (#1, #2, etc.) reports. SAE Worksheets should be sent by Email with Telephone Notification to the Drug Safety Department at:

Telephone #: [redacted]
Email: [redacted]

Drug Safety personnel will be available to answer questions and assist site personnel in documenting SAEs and completing the SAE worksheet.

8.1.3 Investigator Evaluation of Adverse Events

The determination of seriousness, severity and causality must be made by the *physician investigator* who is qualified to review AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. The investigator will evaluate all AEs with respect to seriousness (criteria listed above), severity, and causality (relationship to study drug) according to the guidelines listed below.

Severity will be graded using the RCTC, v2.0. The RCTC is provided in Appendix B. In the event that an AE does not have a RCTC code, the following severity classifications will be used:

SEVERITY

Grade 1: Mild	Causing no limitation of usual activities
Grade 2: Moderate	Causing some limitation of usual activities
Grade 3: Severe	Causing inability to carry out usual activities
Grade 4: Life Threatening*	Potentially life threatening or disabling

* *Note* – a severity assessment of Life Threatening is not necessarily the same as Life Threatening as a "Serious" criteria. The latter means that the event is an immediate threat to life as opposed to a potential threat to life.

8.1.3.1 Assessment of Seriousness

Event seriousness will be determined according to the protocol definition of SAE in Section 8.1.1.

8.1.3.2 Assessment of Severity

Event *severity* will be assigned according to the RCTC, v2.0.

8.1.3.3 Assessment of Causality

The investigator is required to provide an assessment of causality or relationship of AEs to the study drug based on 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified; and 3) biological plausibility. The causality assessment categories that will be used for this study are described below.

Note: If a causality assessment is not provided, a possible relationship will be assumed for regulatory reporting purposes.

Causality assessments that are considered **Not Related** to study drug:

None: The event is related to an etiology other than the study drug (the alternative etiology must be documented in the subject's medical record).

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.

Causality assessments that are considered **Related** to study drug:

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Probable: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Definite: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

***Note* – ICH guidelines (3/95) clarify "reasonable causal relationship" to mean, "that there are facts (evidence) or arguments to suggest a causal relationship."**

8.1.4 Follow-up of Adverse Events

Adverse events will be captured from start of study drug treatment through Day 94. AEs are followed until final outcome is known or until the end of the study Day 94. AEs that are not resolved as of Day 94 are recorded on the AE eCRF as ongoing and in the outcome field as Not Recovered/Not Resolved.

SAEs that have not resolved by Day 94 are followed until final outcome is known. If it is not possible to obtain a final outcome for a SAE (e.g., the subject is lost to follow-up), the reason a final outcome could not be obtained will be documented by the investigator.

Pregnancy:

All reports of pregnancy, or partner pregnancy, occurring after treatment with study drug and up to Day 94 must be reported via the Pregnancy Report form to Safety as per Section 8.1.2. Pregnancy itself is not an AE or SAE. However, any events arising during the pregnancy will be assessed and reported accordingly as an AE or SAE. A spontaneous abortion is always considered to be an SAE and shall be reported on the SAE Worksheet. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the investigator will be reported to Safety. All reported pregnancy cases will be followed up until outcome.

8.1.5 Post Study SAEs

SAEs that occur after the Day 94 visit that are assessed by the investigator to be possibly, probably, or definitely related to study drug must be reported to Safety on a SAE Worksheet, as described in Section 8.1.2. Post study SAEs will not be documented on the AE eCRF.

8.1.6 Reporting to the Institutional Review Board/Independent Ethics Committee

All SAEs that are considered unexpected and related to the investigational drug will be reported by Vizuri Health Sciences/designee as 15-Day (Expedited) reports to the regulatory authority AND to all participating investigators. Each investigator must notify the IRB/IEC responsible for reviewing the study at their site of all 15-Day Reports. Expected and unrelated SAEs will be reported periodically.

8.2 LABORATORY TESTS

Clinical laboratory tests (Appendix A) will be performed at Screening to determine eligibility and on Days 5 and 94 as outlined in Section 6.0.

All female subjects who are biologically capable of having children will have a serum pregnancy test at screening and urine pregnancy test prior to dosing on Day 1. The results of the pregnancy tests must be confirmed to be negative before administration of study drug. FSH testing will be performed on postmenopausal women for up to 2 years after cessation of menses to confirm postmenopausal status.

9.0 DATA ANALYSIS METHODS

9.1 DETERMINATION OF SAMPLE SIZE

A sample size analysis has been performed and suggests that a sample size of 40 evaluable subjects per each of the three study arms will appropriately power this study.

9.2 RANDOMIZATION AND BLINDING

Treatment assignment for all subjects enrolled in this study will be double-blind; the subjects and all site personnel and CRO personnel (with the exception of the Medical Monitor providing safety oversight) involved in this study will not know the treatment given to any subject. Every effort should be made to maintain the study blind.

9.3 ANALYSIS SETS

The following three analysis sets will be defined for this study:

The intent-to-treat (ITT) set will be defined as all randomized subjects, whether or not they receive study drug.

The modified ITT (mITT) set will be defined as the subset of the ITT subjects that receive at least one dose of study medication and have at least one evaluable post-dosing efficacy endpoint. The mITT set will be defined based on randomized treatment rather than treatment actually received. All efficacy analyses will be carried out using the mITT set.

The safety (SAF) set will be based on the ITT subjects, but will be based on the treatment actually received rather than randomized treatment. All safety analyses will be carried out using the SAF set.

9.4 SUBJECT ACCOUNTABILITY

All subjects who meet the inclusion criteria for the study, sign the informed consent form, and are enrolled and exposed to the study medication will be accounted for in the

analyses. Subjects who are deemed 'screen failures' will not be accounted for in the data presentation of response or safety.

9.5 STATISTICAL METHODS

9.5.1 Analysis of Demographic and Subject Characteristics

Subject demographic characteristics including age, gender, race, weight, and height will be summarized by treatment group. Subject baseline disease characteristics that are relevant to the evaluation of the treatment will be summarized by treatment group.

9.5.2 Treatment Administration/Compliance

The Investigators will be responsible for the storage, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. Subjects may be withdrawn from the study by the Sponsor for non-compliance with the protocol.

9.5.3 Efficacy Analyses

Primary Efficacy Endpoint

The group mean LMS difference between each Active Treatment Arm and the Vehicle Arm for the WOMAC pain score at Day 35 will be tested for significance of difference at a significance value of $p \leq 0.05$.

Secondary Efficacy Endpoints

The group mean LMS difference between each Active Treatment Arm and the Vehicle Arm for the WOMAC stiffness, function and total score at Day 35 will be tested for significance of difference at a significance value of $p \leq 0.05$

Also, the group mean reduction in OA knee pain score on a 100 mm VAS scale for each active treatment arm will be compared to the vehicle arm and tested for significance of difference at a significance value of $p \leq 0.05$

For dose-response estimation:

The group mean LMS difference between the 5% and the 1% Active Treatment Arms for the WOMAC pain, stiffness, function and total score at Day 35 will be tested for significance of difference at a significance value of $p \leq 0.05$

Efficacy analyses will be carried out on the mITT set.

9.5.3.1 Clinical Response

Clinical response will be measured by reduction of WOMAC pain score. In order for a subject to be considered to have successfully obtained a clinical response, the following criteria must be met:

WOMAC pain score reduced to 50% or less of baseline at any of the stated assessment times.

The durability of clinical response up to Day 94 will be evaluated by a tabulation of clinical response at a Days 19, 35, 64, and the Day 94 visit by treatment group. Subjects who have successfully met the above criteria (reduction of a least 50% in NRS pain score) at the Day 5 visit and who remain at least at this reduction of pain score or lower at the Day 35 visit will be considered to have a durable clinical response. Subjects who at the Day 35 visit have less reduction in WOMAC in OAKP score than they did at the Day 5 assessment will be considered to have failed to achieve a durable clinical response.

9.5.3.2 Exploratory Analyses

Post hoc tests may be performed to test for differences in the efficacy endpoints between the CGS-200-0 (Vehicle), CGS-200-1 and CGS-200-5 treatment groups for exploratory purposes.

9.5.4 Tolerability Analyses

The primary tolerability endpoint will be tolerability of the formulations on each of Days 1, 2, 3, and 4. On each of these days, subjects will report an NRS score for burning / stinging at the application site pre-treatment and during treatment, and a

pre-treatment and during treatment pruritus score. Pre-treatment and during treatment erythema and scaling scores will be recorded by clinic staff assigned to the study. This will be done at 0, 15, 30, 60, and 90 minutes after application to capture time points during treatment and after washing the application site. The score for each of the above tolerability variables will be entered as a value at each assessment time. For each subject an "area under the curve" (AUC) calculation will be performed in 90 minute intervals for each score value. The AUC's for tolerability variables combined will be compared between the CGS-200-5-and CGS-200-0 treatment groups.

9.5.5 Safety Analyses

9.5.5.1 Adverse Events

The incidence of all reported AEs and treatment-emergent AEs (TEAE) will be tabulated. A TEAE is defined as an event that first occurs or worsens in intensity after the administration of study drug. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of the AE will be graded using the RCTC v2.0 whenever possible. For AEs that are not included in the RCTC v2.0, the grading categories (mild, moderate, severe, and life-threatening) will be used and equated to the respective RCTC grade (Grades 1, 2, 3, and 4). For incidence reporting, if a subject reports more than one AE that is coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term.

An overview of AEs, which includes subject incidence of TEAEs, treatment-related AEs, severity of AEs, SAEs, deaths, and AEs leading to discontinuation, will be presented. For AEs presented by severity, the worst severity during the study will be presented for each subject. The subject incidence of TEAEs will be summarized by system organ class and preferred term. The subject incidence of treatment-related AEs and RCTC v2.0 toxicity grade will be summarized by preferred term.

9.5.6 Vital Signs

Descriptive summaries of the vital signs (both raw and change from baseline values) including blood pressure, heart rate, respiratory rate, and body temperature will be prepared for each dose group. Descriptive statistics for quantitative variables will include sample size, mean, standard deviation, standard error, median, minimum, and

maximum. The 95% confidence interval of the mean will be constructed if it is appropriate (when there is more than 1 subject in a cohort).

Vital sign values will be classified as low, normal or high based on the cut-off points defined below, and the data will be summarized by presenting shift tables from baseline to each post-baseline visit. For Baseline vital sign measurements:

Measurement	Lower	Upper	Unit
Temperature	<35.0	>38.0	C
Systolic Blood Pressure (BP)	<110	>135	mmHg
Diastolic BP	<65	>85	mmHg
Heart Rate	<50	>110	beats/min
Respiratory Rate	<12	>20	breaths/min

For Post-baseline vital sign measurements:

Measurement (unit)	Low	High
Systolic Blood Pressure (mm Hg)	≥ 20 point decrease from baseline	≥ 20 point increase from baseline
Diastolic Blood Pressure (mm Hg)	≥20 points decrease from baseline	≥ 20 point increase from baseline
Pulse (beats per minute (bpm))	< 50 and decrease from baseline ≥ 15	> 100 and increase from baseline ≥ 15
Temperature (C)	<35	>38
Respiratory Rate (breaths per min)	<12	>20

9.5.7 Interim Analyses

Interim analyses will be performed at Days 19, 35, and 64 per 9.5.3 and 9.5.3.1 above,

9.5.8 Procedures for Missing, Unused and Spurious Data

Missing values will not be substituted by estimated values but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

9.5.9 Rules for Excluding Subjects from Analysis

All dosed subjects will be included in the analyses of safety. The sponsor will make any decisions regarding whether any subjects or any individual values belonging to a subject will be excluded from the efficacy evaluations when the protocol violation is considered to have a negative impact on the scientific aspects and interpretation of the study results. If the subject has received any study drug, all available safety data will be used. The reason(s) for any exclusion will be described in the report.

9.5.10 Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

10.0 CLINICAL STUDY ADMINISTRATION

10.1 INFORMED CONSENT

A copy of the proposed informed consent document must be submitted to the sponsor for review and comment prior to submission to the reviewing Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local and institutional regulations or requirements.

The study will be completely explained to each prospective study subject. Each subject found to be eligible for the study must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information), using the IRB/IEC-approved consent form, prior to his or her enrollment in the study (i.e., before any protocol-dictated procedures that are not part of normal patient care are performed).

10.2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE REVIEW AND APPROVAL

The investigator shall assure that an IRB/IEC, constituted in accordance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), will provide initial and continuing review of the study.

The investigator should provide the sponsor with a list of IRB/IEC members or IRB assurance number. Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol and the informed consent form will be in the possession of the investigator and the sponsor/designee, before the study is initiated. The investigator will transmit the IRB/IEC's unconditional approval statement to the sponsor/designee before study drug supplies are shipped to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

The Principal Investigator must inform the IRB/IEC of:

- Changes in informed consent
- Revisions of other documents originally submitted for review
- Serious and/or unexpected adverse events occurring during the study
- New information that may adversely affect the safety of subjects or the conduct of the study
- Annual update and/or request for re-approval
- Study completion

10.3 PROTOCOL COMPLIANCE

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the sponsor and to the IRB/IEC.

10.4 PROTOCOL REVISIONS

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor. If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

10.5 DATA COLLECTION

All data collected for each study subject will be entered in the eCRF developed in the Clinical Database and approved by the Sponsor. The database will be 21 CFR Part 11-compliant. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. The investigator is responsible for maintaining the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data reported in the eCRF derived from source documents should be consistent with the source documents.

The primary source document for this study will be the subject's medical record. Data for the efficacy and tolerability variables will be recorded on a Data Sheet to be provided by Sponsor or designee and made part of the subject's medical record. The Data Sheet will be similar to a paper CRF and will serve as a "hard copy" source document in case the eCRF becomes damaged or otherwise compromised. If the investigator(s) maintain separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study.

The anonymity of subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on eCRFs and other documents submitted to the sponsor. Documents that identify the subject beyond initials and subject number will not be submitted to the sponsor (e.g.; the signed informed consent document) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Data recorded on source documents will be entered into eCRFs. The investigator must promptly review the completed eCRFs for each subject. A study monitor representing the sponsor will review the source documents against the eCRF on a regular basis through the study period as per the Study Monitoring Plan.

Each eCRF will be electronically signed and dated by the Investigator.

10.6 DATA MANAGEMENT RESPONSIBILITIES

For data coding, the following medical dictionaries will be used:

- AEs and concomitant diseases: MedDRA;
- Concomitant medication: World Health Organization (WHO) – Drug

Visual and computerized methods of data validation will be applied in order to ensure accurate, consistent and reliable data for the subsequent statistical analysis. These

procedures aim to detect out-of-range values, contradictory data, abnormal evolutions over time, and possible undetected protocol violations (eligibility criteria, time and medication compliance, etc.).

Data Management and the study monitor will generate electronic queries for resolution by the site.

The database will be locked in order to protect write access after the following preconditions are fulfilled:

- All data are entered in the database
- All data queries are resolved
- All necessary quality checks, in accordance with appropriate Standard Operating Procedures (SOPs), have been performed
- Decisions have been made and agreed as to the identities of all protocol violators
- All eCRFs have been source verified by the study monitor in the remote data capture (RDC)
- All eCRFs have been approved by the Investigator in the RDC system
- Written authorization from Vizuri Health Sciences is obtained.

Upon completion of the study and resolution of all outstanding queries, Data Management will lock the database and generate the SAS datasets necessary for data analysis and reporting.

The Data Management group will use the Clinical Database for storing and managing all data generated by this trial.

10.7 STUDY MONITORING

The study sponsor, Vizuri Health Sciences, or its designee, will monitor the study. Study monitors representing the sponsor will visit study sites routinely throughout the trial. The sponsor/designee will review eCRFs and compare them with source

documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make eCRFs and source documents available when requested.

In addition, the study may be evaluated by representatives of the regulatory authorities, who will also be allowed access to study documents. The investigators should promptly notify Vizuri Health Sciences or its designee of any audits they have scheduled with any regulatory authority.

The sponsor will promptly notify all investigators of all SAEs requiring expedited reporting that are considered unexpected and associated with the study drug. The investigator must also report these AEs to the IRB/IEC responsible for reviewing the study. SAEs that are expected and unrelated to the study drug will be reported periodically.

If Vizuri Health Sciences, its designee, the investigator, the IRB/IEC or regulatory authority discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between Vizuri Health Sciences and the investigator.

10.8 DRUG ACCOUNTABILITY

Upon receipt, the investigator is responsible for taking an inventory of the study drug. A record of this inventory must be kept and usage must be documented on study drug inventory forms provided by the Sponsor.

10.9 RETENTION OF RECORDS

The investigator shall retain records and source documents pertaining to the study, including any films, tracings, computer discs or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for the record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.10 FINANCIAL DISCLOSURE

The investigator will provide Vizuri Health Sciences sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical trial costs) to allow complete disclosure to regulatory authorities. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for a period of one year following study completion.

10.11 PUBLICATION POLICY

Upon completion of the study, investigators are encouraged to publish the results in recognized scientific journals and at seminars or conferences. For multi-center trials, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center trial results are published or 12 months after the end or termination of the multi-center trial at all sites.

A copy of all manuscripts and abstracts related to the study must be submitted to the sponsor for review and comment at least 30 days prior to submission for publication or for presentation at a scientific meeting. Proposed abstracts and publications will be reviewed promptly. The sponsor may delay publication for up to 90 days to allow the filing of a patent application or for other important reasons. The sponsor also reserves the right to delete from such materials any part or parts deemed to be confidential or proprietary.

10.12 STUDY OR STUDY SITE TERMINATION

If Vizuri Health Sciences, the investigator or regulatory authority discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between Vizuri Health Sciences and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate
- Failure of the investigator to comply with pertinent regulatory authority regulations
- Submission of knowingly false information from the research facility to Vizuri Health Sciences, study monitor, or the regulatory authority
- Insufficient adherence to protocol requirements

11.0 REFERENCES

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APPENDICES

APPENDIX A

LABORATORY TESTS

APPENDIX A: LABORATORY TESTS

Chemistry	**Urinalysis**
Glucose	pH
Sodium	Protein
Potassium	Glucose
Chloride	Ketones
Bicarbonate	Bilirubin
Blood Urea Nitrogen (BUN)	Blood
Creatinine	Urobilinogen
Calcium	Specific gravity
Magnesium	Leucocytes
Phosphorous – inorganic	
Lactate Dehydrogenase (LDH)	
Total Protein	**ACR OA criteria exclusions**
Albumin	IgM-RF
Alkaline Phosphatase (ALK)	ESR
Total Bilirubin	
Alanine Transaminase (ALT)	Uric Acid
Aspartate Transaminase (AST)	
Gamma-Glutamyl Transferase (GGT)	
Creatine Phosphokinase (CPK)	**Pregnancy**
	Serum & Urine Pregnancy (βHCG)
CBC with Automated Differential	
White Blood Cell Count (WBC)	**Follicle-stimulating Hormone (FSH)**
Red Blood Cell Count (RBC)	
Hemoglobin (Hgb)	
Platelet Count	
Automated White Blood Cell Differential	
Neutrophils (% & absolute)	
Lymphocytes (% & absolute)	
Red Cell Indices	
Hematocrit	
MCV	
MCH	
MCHC	

APPENDIX B

RHEUMATOLOGY COMMON TOXICITY CRITERIA V2.0

APPENDIX B: RHEUMATOLOGY COMMON TOXICITY CRITERIA V2.0

Rheumatology Common Toxicity Criteria v.2.0 Based on Woodworth TG, *et al*., 2007.[8] Standardizing assessment of adverse effects in rheumatology clinical trials II. Status of OMERACT Drug Safety Working Group May 2006: OMERACT 8. Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials: Enabling Description of Comparative Safety Profiles for Antirheumatic Therapies				
	1-Mild Asymptomatic, or transient Short duration (<1 week) No change in life style No medication or OTC	**2- Moderate** Symptomatic Duration (1-2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription), Study drug continued	**3- Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/ partial relief May be hospitalized <24hr Temporary study drug discontinuation, or/and dose reduced	**4- Includes Life Threatening** At risk of death Substantial disability, especially if permanent. Multiple meds Hospitalized >24 hr Study drug discontinued
A. ALLERGIC/IMMUNOLOGIC				
A1. Allergic reaction/hypersensitivity (includes drug fever)	Transient rash: drug fever <38°C: transient, asymptomatic bronchospasm	Generalized urticaria responsive to meds; or drug fever > 38°C, or reversible bronchospasm	Symptomatic bronchospasm requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angiodema	Anaphylaxis, laryngeal/pharyngeal oedema, requiring resuscitation
A2. Autoimmune reaction	Serologic or other evidence of autoimmune reaction, but patient asymptomatic: all organ function normal and no treatment is required (e.g. vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g. hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g. transient colitis or anaemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription med. Required, slow	Corticosteroids or other prescription med. With persistent disabling symptoms such as impaired exercise tolerance	N/A
A4. Serum sickness	Transient, non-prescription meds relieve	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required	Major organ dysfunction, requires long-term high-dose immunosuppressive therapy

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
A. ALLERGIC/IMMUNOLOGIC (CONT)				
A5. Vasculitis	Localized, not requiring treatment; or rapid response to meds; cutaneous	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Generalized, parenteral corticosteroids required or/and short duration hospitalisation	Prolonged, hospitalization, ischemic changes, amputation
B. CARDIAC				
B1. Arrhythmia	Transient, asymptomatic	Transient, but symptomatic or recurrent, responds to meds	Recurrent/persistent; maintenance prescription	Unstable, hospitalization required; parenteral meds
B2. Cardiac function Decreased	Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value	Asymptomatic decline of resting ejection fraction ≥20% of baseline value	CHF responsive to treatment	Severe or refractory CHF
B3. Edema	Asymptomatic (e.g. 1 + feet/calves), self-limited, no therapy required	Symptomatic (e.g. 2 + feet/calves), requires therapy	Symptoms limiting function (e.g. 3 + feet/calves, 2 + thighs), partial relief with treatment, prolonged	Anasarca; no response to treatment
B4. Hypertension (new onset or worsening)	Asymptomatic, *transient* increase by > 20 mm Hg (diastolic) or to > 150/100 if previously normal, no therapy required	Recurrent or persistent increase > 150/100 or by > 10 mm Hg (diastolic), requiring and responding readily to treatment	Symptomatic increase >150/100, > 20 mmHg, persistent, requiring multi-agent therapy, difficult to control	Hypertensive crisis
B5. Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic, orthostatic decrease in blood pressure > 20 mm Hg	Symptomatic, without interference with function, recurrent or persistent > 20 mm Hg decrease, responds to treatment	Syncope or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation	Shock

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
B. CARDIAC (CONT)				
B6. Myocardial ischaemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain, transient ECG ST-T changes; treatment relieves	Angina with infarction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infarction, arrhythmia and CHF
B7. Pericarditis/ pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocardiogram, symptomatic NSAID required	Detectable on chest X-ray, dyspnoea; or pericardiocentesis; requires corticosteroids	Pulsus alternates with low cardiac output; requires surgery
B8. Phlebitis/thrombosis/ Embolism (excludes injection sites)	Asymptomatic, superficial, transient, local, or no treatment required	Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required	Deep vein thrombosis requiring anticoagulant therapy	Pulmonary embolism
C. GENERAL (constitutional)				
C1. Fatigue/malaise (asthenia)	Increase over baseline; most usual daily functions maintained, short term	Limits daily function intermittently over time	Interferes with basic ADL, persistent	Unable to care for self, bed or wheelchair bound > 50% of day debilitating, hospitalisation
C2. Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy)	Transient, few symptoms 37.7-38.5°C	Symptomatic, recurrent 38.6-39.9°C. Relieved by meds	≥ 40°C; ≤24h, persistent symptoms; partial response to meds.	≥ 40°C, debilitating, > 24h, hospitalization; no relief with meds
C3. Headache	Transient or intermittent, no meds or relieved with OTC	Persistent, recurring, non-narcotic analgesics relieve	Prolonged with limited response to narcotic medicine	Intractable, debilitating, requires parenteral meds.
C4. Insomnia	Difficulty sleeping, short term, not interfering with function	Difficulty sleeping Interfering with function, use of prescription med.	Prolonged symptoms, with limited response to narcotic meds.	Debilitating, hospitalization; no relief with meds
C5. Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve.	Prolonged symptoms, with limited response to narcotic meds.	Debilitating, hospitalization; no relief with meds
C6. Sweating (diaphoresis)	Episodic, transient	Frequent, short term	Frequent, drenching, disabling	Dehydration, requiring IV fluids/hospitalization 24 hr
C7. Weight gain	5-9.9%	10-19.9%	20-30%	NA
C8. Weight loss	5-9.9%	10-19.9%	20-30%	NA

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
D. DERMATALOGIC				
D1. Alopecia	Subjective, transient	Objective, fully reversible	Patchy, wig used, partly reversible	Complete, or irreversible even if patchy
D2. Bullous eruption	Localised, asymptomatic	Localised, symptomatic, requiring treatment	Generalized, responsive to treatment; reversible	Prolonged, generalized, or requiring hospitalization for treatment
D3. Dry skin	Asymptomatic, controlled with emollients	Symptoms eventually (1-2 wks controlled with emollient	Generalized, interfering with ADL >2 wks, persistent pruritus, partially responsive to treatment	Disabling for extended period, unresponsive to ancillary therapy and requiring study drug discontinuation for relief
D4. Injection site reaction	Local erythema, pain, pruritus, < few days	Erythema, pain, oedema, may include superficial phlebitis, 1-2 wks	Prolonged induration, superficial ulceration; includes thrombosis	Major ulceration necrosis requiring surgery
D5. Petechiae (without vasculitis)	Few, transient asymptomatic	Dependent areas, persistent up to 2 wks	Generalized, responsive to treatment; reversible	Prolonged, irreversible, disabling
D6. Photosensitivity	Transient erythema	Painful erythema and oedema requiring topical treatment	Blistering or desquamation, requires systematic corticosteroids	Generalized exfoliation or hospitalisation
D7. Pruritus	Localised, asymptomatic, transient, local treatment	Intense, or generalized, relieved by systematic medication	Intense or generalized; poorly controlled despite treatment	Disabling, irreversible
D8. Rash (not bullous)	Erythema, scattered macular/papular eruption; pruritus transient; TOC or no meds	Diffuse macular/86papular eruption or erythema with pruritus; dry desquamation; treatment required	Generalized, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalization; or parenteral corticosteroids
D9. Induration/Fibrosis/ Thickening (not sclerodermal)	Localized, high density on palpation, reversible, no effect on ADL and not disfiguring	Local areas < 50% body surface, not disfiguring, transient interference with ADL, reversible	Generalized, disfiguring, interferes with ADL, reversible	Disabling, irreversible, systemic symptoms

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
E. EAR/NOSE/THROAT				
E1. Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function; incomplete response to treatment	Irreversible deafness
E2. Sense of smell	Slightly altered	Markedly altered	Complete loss, reversible	Complete loss, without recovery
E3. Stomatitis	Asymptomatic	Painful, multiple, can eat	Interferes with nutrition, slowly reversible	Requires enteral support; residual dysfunction
E4. Taste disturbance (dysgeusia)	Transiently altered; metallic	Persistently altered; limited effect on eating	Disabling, effect on nutrition	NA
E5. Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness
E6. Voice changes (includes hoarseness, loss of voice, laryngitis	Intermittent hoarseness, able to vocalise	Persistent hoarseness, able to vocalize	Whispered speech, slow return of ability to vocalise	Unable to vocalize for extended period
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition
F. EYE/OPHTHALMOLOGIC				
F1. Cataract	Asymptomatic, no change in vision, non-progressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	NA
F2. Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	NA
F3. Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	NA
F4. Retinopathy	Asymptomatic, non- progressive, no treatment	Reversible change in vision; readily responsive to treatment	Disabling change in vision ophthalmological findings reversible, sight improves over time	Loss of sight

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
F. EYE/OPHTHALMOLOGIC (CONT)				
F5. Vision changes (e.g. blurred, photophobia, night blindness, vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	Loss of sight
F6. Xerophthalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight
G. GASTROINTESTINAL				
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring iv support	Requires hospitalization for nutritional support
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation requiring medical intervention	Bowel obstruction. Surgery required.
G3. Diarrhea	Transient, increase of 2-3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4-6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds.	Increase > 6 stools/day, associated with disabling symptoms, e.g. incontinence, severe cramping, partial response to treatment.	Prolonged, dehydration, unresponsive to treatment, requires hospitalization.
G4. Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds, relieved by meds	Persistent despite treatment, interferes with function, associated with GI bleeding	NA
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-define aetiology)	Asymptomatic, endoscopic finding, haemocult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤2 units needed; responds to treatment	Haematemesis, transfusion 3-4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalisation
G6. Haematochezia (rectal bleeding)	Haemorrhodial, asymptomatic, no transfusion	Symptomatic, transfusion ≤2 units, reversible	Recurrent, transfusion > 3-4 units	> 4 units, hypotension, requiring hospitalisation

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
G. GASTROINTESTINAL (CONT)				
G7. Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persistent >2 wks, symptoms interfere with function	Progressive, hepato-renal, anasarca, pre-coma or coma
G8. Nausea, or nausea/vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds.	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic iv fluids	Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management
G9. Pancreatitis	Amylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, haemorrhage (acute circulatory failure)
G10. Proctitis	Perianal pruritus, haemorrhoids (new onset), transient, or intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with haemorrhage, infection, surgery required
H. MUSCULOSKELETAL				
H1. Avascular necrosis	Asymptomatic MRI changes, non-progressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible
H2. Arthralgia	Intermittent transient symptoms, no meds or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds impairs function	Debilitating, hospitalization required for treatment
H3. Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, responds to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	NA
H4. Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non- narcotic); minor effects on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
I. NEUROPSYCHIATRIC				
I1. Anxiety or Depression (mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms, partial or no response to meds, limits daily function	Suicidal ideation or danger to self
I2. Cerebrovascular ischaemia	NA	Single transient ischaemic event, responsive to treatment	Recurrent transient ischaemic events	Cerebrovascular vascular accident with permanent disability
I3. Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent, or worsening objective symptoms; interferes with routine daily routine	Debilitating/disabling and permanent; toxic psychosis
I4. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obtundation, stupor	Coma
I5. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings or organic cause	NA
I6. Insomnia (in absence of pain)	Occasional difficulty sleeping, transient intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	NA
I7. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged interfering with relationship	NA
I8. Peripheral motor neuropathy	Subjective or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis
I9. Peripheral sensory neuropathy (sensory disturbance)	Subjective symptoms without objective findings, transient, not interfering with function	Objective sensory loss, persistent, not interfering with function	Prolonged sensory loss or paraesthesias interfering with function	NA

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
I. NEUROPSYCHIATRIC (CONT)				
I10 Seizure	NA	Recurrence of old seizures, controlled with adjustment of medication	Recurrence/exacerbation with partial response to medication	Recurrence not controlled, requiring hospitalization; new seizures
I11 Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial response to medication	Debilitating without response to medication, hospitalisation
J. PULMONARY				
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal 0_2	Requires ventilator assistance
J2. Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating
J3. Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal 0_2 relieves	Symptomatic at rest, debilitating, requires constant nasal 0_2
J4. Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitation, requiring hospitalisation
J5. Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including 02	Debilitating, not reversible; or requiring assisted ventilation
J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity — DLCO)	76-90% of pre-treatment value	51-75% of pre-treatment value	26-50% of pre-treatment value	≤25% of pre-treatment value

LABORATORY DATA

K. HAEMATOLOGY				
	1- Mild	**2- Moderate**	**3- Severe**	**4- Includes Life Threatening**
K1. Hgb (g/dl) decrease from pre-treatment	1.0-1.4	1.5-2.0	2.1-2.9, or Hgb<8.0, >7.0	≥ 3.0; or Hgb < 7.0
K2. Leukopenia (total WBC) X 1000	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
K3. Neutropenia (X 1000)	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
K4. Lymphopenia (X 1000)	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
K5. Platelets (X 1000)	75-LLN	50-74.9	20-49.9; platelet transfusion required	< 20; recurrent platelet transfusions
L. CHEMISTRY				
L1. Hypercalcaemia (mg/dl)	1.1 X ULN — 11.5	11.6 — 12.5	12.6 — 13.5; or symptoms present	> 13.5; or associated coma
L2. Hyperglycemia (mg/dl) Fasting	140 — 160	161 — 250	251 — 500	> 500, or associated with ketoacidosis
L3. Hyperkalaemia (mg/dl)	5.5 – 5.9	6.0 – 6.4	6.5 – 7.0 or any ECG change	> 7.0 or any arrhythmia
L4. Hypocalcaemia (mg/dl)	0.9 X LLN – 7.8	7.7 – 7.0	6.9 - 6.5; or associated with symptoms	< 6.5 or occurrence of tetany
L5. Hypoglycemia (mg/dI)	55 – 64 (no symptoms)	40 – 54 (or symptoms present)	30 – 39 (symptoms impair function)	30 or coma
L6. Hyponatraemia- (mg/dI)	-	125 – 129	120 – 124	< 120

	1- Mild	2- Moderate	3- Severe	4- Includes Life Threatening
L. CHEMISTRY (CONT)				
L7. Hypokalaemia-(mg/dl)	-	3.0 – 3.4 2.0 -4.0 X ULN	2.5 – 2.9 4.0 X ULN with weakness but without life-threatening signs or symptoms	< 2.5 > 4.0 X ULN with signs or symptoms of rhabdomyolysis or life-threatening
L8. CPK (also if polymyositis-disease	1.2 – 1.9 X ULN	2.0 – 4.0 X ULN	> 4.0 X ULN with weakness but without life-threatening signs or symptoms	> 4.0 X ULN with signs or symptoms of rhabdomyolysis or life-threatening
L9. Serum uric acid	1.2 – 1.6 X ULN	1.7 – 2.9 X ULN	3.0 – 5.0 X ULN or gout	NA
L10. Creatinine (mg/d1)	1.1-1.3 XULN	1.3 – 1.8 X ULN	1. – 3.0 X ULN	> 3.0 X ULN
L11. SGOT (AST)	1.2 – 1.5 X ULN	1.6 – 3.0 X ULN	3.1 – 8.0 X ULN	> 8.0 X ULN
L12. SGPT (ALT)	1.2 – 1.5 X ULN	1.6 – 3.0 X ULN	3.1 – 8.0 ULN	> 8 X ULN
L13. Alkaline Phosphatase	1.1 – 2.0 X ULN	2.1 – 3.0 X ULN	3.1 – 5.0 X ULN	> 5.0 X ULN
L14. T. bilirubin	1.1-1.4 XULN	1.5 – 1.9 X ULN	2.0 – 3.0 X ULN	> 3.0 X ULN
L15. LDH	1.3 – 2.4 X ULN	2.5 – 5.0 X ULN	5.1 – 10 X ULN	> 10 XULN
M. URINALYSIS				
M1. Haematuria	Micro only	Gross, no clots	Clots, transfusion < 2 units	Transfusion required
M2. Proteinuria (per 24 h)	300 – 500 mg (tr/1+)	501 – 1999 mg (2+)	2 – 5.0 g (3+) nephritic syndrome	5.0 g (4+) anasarca
M3. WBC in Urine	NA	NA	Indicating acute interstitial nephritis	Associated with acute renal failure
M4. Uric acid crystals	Present without symptoms	NA	With stones or symptoms of stones (eg renal colic)	Causing renal outflow obstruction and hospitalization

APPENDIX C

SCHEDULE OF EVENTS

APPENDIX C: SCHEDULE OF EVENTS

Assessment	**SCR**	**Treatment Days**				**Follow-up Period Days**					
TIMEFRAME	Within 28 days of Day 1	D1	D2	D3	D4	D5 (Post Treat Day 1)	D19± 3d (Post Treat Week 2)	D35± 3d (Post Treat Week 4)	D64± 3d (Post Treat Week 8)	D94± 3d (Post Treat Week 12)	Unscheduled, Early Termination, SAE[l]
Clinic visit	x	x	x	x	x	x	x	x	x	x	x
Informed Consent	x										
Inclusion / Exclusion	x										
Demographics	x										
Medical & Medication History	x										
Randomization		x									
Physical exam	x										x
Height and Weight[a]	x										
Vital Signs[b]	x	x	x	x	x	x				x	x
Knee X-rays[c]	x										
12-lead ECG[d]	x										
Clinical lab tests[e]	x					x		x		x	x
Pregnancy or FSH Test[f]	x	x									
Application Site Pain, Erythema, Scaling, Pruritus Assessment[g]	x	x	x	x	x	x	x	x	x	x	x
Exploratory Assessment of OA Knee Pain[h]	x	X									
VAS OA Knee Pain Assessment[i]		x	x	x	x	x	x	x	x	x	x
WOMAC[j]	X	x				x	x	x	x	x	x
Drug administration		x	x	x	x						
Assess. Of Concomitant Medications[k]	x	x	x	x	x	x	x	x	x	x	x
AE Assessments		x	x	x	x	x	x	x	x	x	x
Study Exit										x	

Schedule of Events (Continued)

a. Height and weight obtained at Screening.

b. Vital signs include temperature, blood pressure, heart rate and respiratory rate. Performed at Screening, on Days 1-4 at pre-dose and at 90 minutes (± 5 min) after applying study drug to knees, and at Follow-up on Day 5 and 94.

c. Knee X-rays of both knees must be obtained unless films/images performed within 6 months before screening. Copies of film and results will be requested.

d. Standalone 12-lead ECG performed at Screening.

e. Clinical laboratory tests include (Appendix A):

Hematology: full blood count including RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, WBC, differential white cell count, platelet count (Screening, Day 5, Day 35 and Day 94);

Erythrocyte sedimentation rate (Screening only);

Chemistry: BUN, creatinine, uric acid, bilirubin (total), sodium, potassium, calcium, magnesium, phosphorous (inorganic), chloride, bicarbonate, ALK, AST (SGOT), ALT (SGPT), LDH, GGT, CPK, albumin, total protein, and glucose (Screening, Day 5, Day 35 and Day 94);

IgM RF (Screening only);

Urinalysis: pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, specific gravity, leucocytes (Screening, Day 5, Day 35 and Day 94). Clinically significant abnormal dipstick results will require microscopic analysis.

f. Serum pregnancy test at Screening and urine pregnancy test at baseline on Day 1 for premenopausal women; FSH (follicle stimulating hormone) test at Screening to confirm postmenopausal status (females only) for up to 2 years after cessation of menses.

g. Application site pain will be assessed on NRS (0-10); application site erythema/edema will be assessed using modified categorical Draize test (0-3). Scaling and pruritus will also be scored on a similar categorical scale (0-3). Scoring for application site pain (not related to knee pain) will be performed on drug administration Days 1-4 (pre-application [≤ 30 min], and at 15 (± 5 min), 30 (± 5 min), 60 (± 5 min) and 90 minutes (± 5 min) after application) and on Days 5, 19, 35, 64 and 94. Application site skin reactions (erythema, edema, scaling, pruritus) will be assessed on drug administration Days 1-4 at pre-application (≤ 30 min), and at 15 (± 5 min), 30 (± 5 min), 60 (± 5 min) and 90 minutes (± 5 min) after application), and on Days 5 (24 hrs [+/- 4 hrs]), 19 (+/- 3 days), 35 (+/- 3 days), 64 (+/- 3 days) and 94 (+/- 3 days). (Appendix E and Appendix F)

h. Exploratory assessment of OA knee pain (average daily pain and daily worst pain) at Screening and Day 1 (pre-application [≤30 min]) (Appendix D).

i. OA Knee pain to be scored on 100 mm VAS scale (Appendix G) pre-treatment (≤ 30 min) on Days 1, 2, 3 and 4 and also on clinic visits at Days 5 (24 hrs [+/- 4 hrs]), 19 (+/- 3 days), 35 (+/- 3 days), 64 (+/- 3 days) and 94 (+/- 3 days).

j. WOMAC Pain, Stiffness, and Physical Function will be performed at Screening and on Day 1 prior to drug administration (≤ 30 min) and on Days 5 (24 hrs [+/- 4 hrs]), 19 (+/- 3 days), 35 (+/- 3 days), 64 (+/- 3 days) and 94 (+/- 3 days).

k. Document all medications taken within 90 days of the Screening Visit through Day 94.

l. Refer to Section 6.5 for assessments to be completed at time of SAE, early termination or unscheduled visit.

APPENDIX D

EXPLORATORY ASSESSMENT OF OSTEOARTHRITIS KNEE PAIN

APPENDIX D: EXPLORATORY ASSESSMENT OF OSTEOARTHRITIS KNEE PAIN

Obtained at Screening and pre-dose on Day 1.

On a scale from 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your **AVERAGE DAILY PAIN**

0	1	2	3	4	5	6	7	8	9	10
No										Worst Pain
Pain										Imaginable

On the same scale, how would you rate your **DAILY WORST PAIN**

0	1	2	3	4	5	6	7	8	9	10
No										Worst Pain
Pain										Imaginable

APPENDIX E

VAS OA KNEE PAIN

APPENDIX E: VAS OA Knee Pain

Obtained on Days 1-4: Pre-application (≤ 30 min), and on Days 5, 19, 35, 64 and 94.

VAS Pain Scale (100 mm)

On the line below make a mark that represents your present level of pain for your RIGHT knee

no pain — worst pain imaginable

On the line below make a mark that represents your present level of pain for your LEFT knee

no pain — worst pain imaginable

APPENDIX F

ASSESSMENT OF BURNING / STINGING PAIN

APPENDIX F: ASSESSMENT OF BURNING / STINGING PAIN

Obtained on Days 1-4: Pre-application (< 30 min), and at 15 (+ 5 min), 30 (+ 5 min), 60 (+ 5 min), and 90 minutes (+ 5 min) after application, and on Days 5, 19, 35, 64 and 94.

Assessment of Burning / Stinging Pain

The question below refers to BURNING OR STINGING PAIN that you may be feeling right now affecting the skin in the area around your knees.

On a scale from 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain RIGHT NOW in your RIGHT KNEE? (Please circle the number)

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

On a scale from 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain RIGHT NOW in your LEFT KNEE? (Please circle the number)

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

APPENDIX G

ASSESSMENT OF SIGNS AND SYMPTOMS

APPENDIX G: ASSESSMENT OF SIGNS AND SYMPTOMS

Obtained on Days 1 – 4: Pre-application (≤ 30 min), and at 15 (± 5 min), 30 (± 5 min), 60 (± 5 min), and 90 minutes (± 5 min) after application, and on Days 5, 19, 35, 64 and 94.

Assessment of Signs and Symptoms

Right Knee

Scaling (Circle Response):

0 = None: no evidence of scaling
1 = Mild: mainly fine scales predominate
2 = Moderate: somewhat coarser scales
3 = Severe: coarse, thick scales; rough surface

Erythema (Circle Response):

0 = None: no evidence of redness
1 = Mild: barely perceptible redness
2 = Moderate: obvious redness, possible presence of edema
3 = Severe: bright red, possible edema

Pruritus (Circle Response):

0 = None: no itching
1 = Mild: occasional, slight itching
2 = Moderate: frequent or constant itching; does not disturb sleep
3 = Severe: bothersome itching; disturbs sleep

Left Knee

Scaling (Circle Response):

0 = None: no evidence of scaling
1 = Mild: mainly fine scales predominate
2 = Moderate: somewhat coarser scales
3 = Severe: coarse, thick scales; rough surface

Erythema (Circle Response):

0 = None: no evidence of redness
1 = Mild: barely perceptible redness
2 = Moderate: obvious redness, possible presence of edema
3 = Severe: bright red, possible edema

Pruritus (Circle Response):

0 = None: no itching
1 = Mild: occasional, slight itching
2 = Moderate: frequent or constant itching; does not disturb sleep
3 = Severe: bothersome itching; disturbs sleep