DUHS IRB Application (Version 1.29)

General Information

*Please enter the full title of your protocol:		
Efficacy of a topical pain relief spray containing herbal oil Extracts (Bonipar) among individuals with acute and chronic musculoskeletal pain		
***Please enter the Short Title you would like to use to reference the study:**		
Bonipar for Acute & Chronic Muskuloskeletal Pain * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

Research Summary

State your primary study objectives

The objective of this study is evaluate the efficacy and onset of action of Bonipar, a topical analgesic derived from a variety of essential oils, in controlling pain in patients with acute and chronic musculoskeletal pain, as compared to the topical NSAID, diclofenac topical solution 1.5%.

State your secondary study objectives

none

Please select your research summary form:

Standard Research Summary Template

This is the regular (generic) research summary template which is required for all regular applications (unless your protocol fits under the other research summary templates in this category). Use of these instructions is helpful for ensuring that the research summary contains all necessary elements.

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

To evaluate the efficacy and onset of action of Bonipar in controlling pain in patients with acute and chronic musculoskeletal pain syndromes.

Background & Significance

- Should support the scientific aims of the research

Acute and chronic pain patients with musculoskeletal-skeletal pain are treated in many ways. The use of pharmacological agents in treating these is frequently associated with unacceptable complications: non-selective nonsteroidal anti-inflammatory drug (NSAID) may cause serious gastrointestinal disorders including hemorrhage requiring hospitalization and sometimes death; COX2-selective NSAIDS may also cause GI complications but more especially may cause coronary events especially in hypertensive patients; acetaminophen and related drugs may cause hepatic dysfunction and occasionally liver failure and opioids are usually associated with drug misuse, drug abuse, drug diversion and addiction which are currently assuming epidemic proportions in the USA. As a consequence of these undesirable pharmacological issues, the search for safe and effective drugs to treat both acute and chronic musculoskeletal pain continues.

Topical analgesic have a place in managing musculoskeletal pain but their scientific efficacy has usually been anecdotal and seldom subjected to investigational scrutiny. These topical agents are relatively safe but may still have adverse effects by virtue of their pharmacological compositions. The use of natural compounds e.g. essential oils from selective herbal extracts have been used by many persons from tropical and subtropical regions for medicinal purposes including pain.

Thus, the objective of this study is to evaluate the efficacy and onset of action of Bonipar, a topical analgesic derived from a variety of essential oils, in controlling pain in patients with acute and chronic musculoskeletal pain, as compared to the topical NSAID, Diclofenac topical solution 1.5%.

Design & Procedures

- Describe the study, providing detail regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

This study is a non-inferiority study comparing efficacy and onset of action between the herbal extracts topical solution, Bonipar, and diclofenac sodium topical solution, diclofenac topical solution 1.5% (approved by the FDA as a topical analgesic). Approximately 240 Duke patients will be recruited from Duke Pain Clinic, and selected Duke primary care practices, as well as the Durham VA site. Individuals who report acute (less than 3 months duration) or chronic musculoskeletal pain of any intensity will be considered for enrollment into the study. After obtaining consent, eligible subjects will be will be randomized to receive Bonipar or diclofenac topical solution 1.5%.

For study purposes, diclofenac topical solution 1.5% will be used off-label—that is, it may be used for pain not known to be caused by osteoarthritis. However, this study does not aim to identify a new indication for diclofenac topical solution 1.5%.

Baseline Assessments

The following baseline assessments will be completed prior to administration of study drug:

· Review of medical history

· Although the risk of serious side effects is low when diclofenac is applied to the skin, pregnant women will be excluded from this study. Urine pregnancy screening will be conducted for all female subjects of childbearing potential.* Women who have a positive pregnancy test would be excluded.

· Limited skin examination and blood pressure measurement. We will exclude patients with SBP > 160 and DBP > 95 at screening.

· Collect pain information such as onset, pain intensity 24 hours prior and immediately before study drug application

*Female subjects are considered "of child-bearing potential" if they (a) are anatomically

and physiologically capable of becoming pregnant and (b) they will be, or could possibly

be, engaging in sexual activity with males while study interventions that pose the

possibility of harm to a fetus are occurring. Note that this time period also includes any

time after study activities have ended where the protocol specifies the use of

contraception.

Dose, Delivery and Dispensing

After obtaining consent, subjects will be randomized to one of two study groups (Bonipar or diclofenac topical solution 1.5%), utilizing a predetermined randomization schedule in a 1:1 ratio.

The study drug, Bonipar, is stored in an opaque plastic bottle so that the contents may be protected from both direct and indirect sunlight because it is likely that sunlight could result in the degradation and/or decomposition of some of the essential oils contained in Bonipar. For blinding purposes, Diclofenac topical solution 1.5% will be stored in the same opaque plastic bottle. The bottles will be labeled either "Drug A" or Drug B" according to their designation, lot #, BUD (beyond use dating), dosing instructions, and FDA statement "Caution: New Drug—Limited by Federal law to investigational use". Thus, the drugs would be blinded to both the patients and to the investigators. Only the unblinded Clinical Research Coordinator (CRC) will have access to the randomization scheme and will have the knowledge of the dispensed drugs. To avoid any bias, the principal investigator would strongly advise the study technicians not to communicate any information regarding the 2 drugs to their investigator colleagues.

All subjects will be instructed on the application of the assigned drug. Subjects will be asked to apply the study drug 2 pumps 2 times a day to be applied topically on the affected area during a one week treatment period. Application instructions will be provided to the subjects. Prior to the first use, the study coordinator will prime the pump by pushing down fully 4 times, and to discard any solution to ensure an accurate dose is delivered during first use.

Study Drug Application at Home

Written study drug application instructions, storage instructions, and a study diary will be provided to all subjects at the time of discharge from the clinic.

At home, subjects will continue to apply the study drug twice a day. In the 1 week diary, subjects will record daily drug application, pain scores before and after application and any other oral

pain medication taken. Subjects are permitted in the study to take acetaminophen (325 to 650 mg tablet up to 4 times a day) if pain persists even with the study drug application.

Subjects will be instructed to observe the following instructions:

1. Please wash and dry hands before and after use.

2. Do not apply to skin with open wounds, or blistered or inflamed areas of the skin.

3. Avoid contact with your eyes and mucous membranes.

4. Do not apply external heat.

5. Do not shower for at least 30 minutes after applying study drug.

6. Do not wear clothing over the treated area until the area is dry.

7. Do not take other NSAID (like aspirin, ibuprofen, naproxen, ketorolac, diclofenac, etc.) while enrolled on this study. Please contact the study doctor or research staff if you are unsure.

8. Keep the bottle away from direct sunlight.
9. Protect the treated area from natural or artificial sunlight.
10. Wait until the treated area is dry before applying sunscreen, insect repellant, lotion, moisturizer or cosmetics to the same area.
11. Avoid skin-to-skin contact between other people and the treated area until the treated area is completely dry.

Follow- Up
All subjects will be asked to come back for a study visit at one week (+/- 1 day) after initial dosing for assessment, to return the completed diary and remainder of the study drug. If subjects are not able to physically return for the follow-up visit, a remote video follow-up visit can be done for the required study assessments. Remote visits will not be audio or video recorded. Subjects completing a remote video follow-up visit must return to clinic for a physical follow-up visit when able. Subjects who do not receive adequate pain relief during the study may opt to drop out and resume taking their prior prescribed medications or they may return to their primary care physician. If this occurs, subjects will be asked to discard any unused study drug.

DURATION OF STUDY:
This study will be for 1 weeks from initial study drug application.

OUTCOME MEASURES:
The following assessments would be determined:

1. Numerical Pain Rating Scale (NPRS) score at:
    a. time of enrollment
    b. 24-hours earlier
    c. 1 week later twice daily (am and pm)
2. Time of Onset of Action of Bonipar measurement
3. Report of any adverse effects or complications.

Protected health information (PHI) will be kept confidential as required by law. Some information collected about this research study may be kept in a research study record separate from the medical record, and some research information may also be part of the medical record. Except when required by law, subject will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). For records disclosed outside of DUHS, subject will be identified using a unique code number. The unique code and date of birth will be reported on the Case Report Forms (CRF). The key to the code will be kept in a locked file.

If the patient is not eligible or does not want to participate in the study their PHI is shredded and destroyed. For consented patient, PHI is kept in research office in a locked desk or cabinet when not being used by the research staff. The information we review are on individual computers which are password protected. The office doors are kept locked when no one from the research staff is in the office. The only people who have access to the rooms are the research staffs which are listed on the key personnel sheet. Study records will be retained with Duke for at least six years after the study is completed.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

INCLUSIONARY CRITERIA:

1. Subject with acute and chronic localized musculoskeletal pain
2. Ages 18 to 80 years
3. Female subjects of childbearing age* must have a negative pregnancy test

Female subjects of childbearing age who are sexually active must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical

sterilization (such as tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD).

4. Willing to provide written informed consent
5. Patients taking opioid or NSAID for their musculoskeletal pain may be included if pain is inadequately controlled

*A woman of childbearing age is post-menarche and premenopausal, physiologically capable of fertilization and pregnancy.

EXCLUSIONARY CRITERIA:

1. Use of any topical agents on the affected area within 3 days of screening
2. Subject with active skin lesions or active skin disease or with current cutaneous manifestations of systemic illnesses
3. Subject with known uncontrolled diabetes at time of screening (A1C of more than 9)
4. Subject with uncontrolled hypertension at time of screening (SBP > 160 and DBP > 95)
5. Subject with active uncontrolled GERD (defined as more than 2 episodes per week) or history of peptic ulcer disease
6. Subject with active cancer or active spinal cord lesions
7. Recent spine surgery (within 3 months of screening)
8. Subject with allergies to diclofenac or to other non-steroid anti-inflammatory drugs (NSAID)
9. Known allergies to any oils, methyl salicylate and/or camphor
10. Subject is pregnant or lactating
11. Subjects who, within the past 3 months, have history of heart attack, stroke, or blood clot
12. Recent coronary artery bypass graft surgery (CABG) (i.e., within 6 months of screening)
13. Subject with history of alcohol or drug abuse within the past 3 months
14. Subject with history of severe liver or kidney disease or any other medical condition within 3 months of screening that may interfere with the subject's ability to participate in the study as determined by the Investigator

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

To screen for eligible patients, a request for Waiver or Alteration of Consent and HIPAA Authorization will be obtained prior to start of study. An advertisement flyer and advertisement will be used. MyChart messages to subjects will be used, facilitated by DOCR. We gather screening information by reviewing MD appointments, medical history and clinical diagnosis from Epic Maestro Care, from Duke clinician referrals, and/or utilizing the phone script.

Patient's research opt-out status will be noted prior to approach. If patient expresses the would like to opt-out of all research contact, the PI or designee will complete the REDCap Survey (https://redcap.duke.edu/redcap/surveys/?s=9NX7DY7DXX) to convey the patient's information to the appropriate Maestro Care Analyst team and refer the patient to the Notice of Privacy Practices (https://www.dukehealth.org/privacy).

If the opt-out status is not present and the subject expresses interest in learning more about the study, the PI or designee will commence in approaching subject.

If patients are missed for in-person approaches, a phone script will be utilized to give interested patients an opportunity to hear about the study via phone. After conversing via phone, and if the patient is still interested, a copy of the ICF will be mailed or emailed to the patient to read over. The study team will work with interested patients to schedule a time to come in, or piggy back at their next clinic visit.

No study-specific procedures will be performed until consent has been given. The Investigator will retain an original signed consent form and the subject will receive a copy to take home. If after speaking with the potential subject they would not like to participate in the study, we destroy all information by redacting PHI or shredding it.

COMPENSATION

After the 1 week follow-up study visit and return of the study diary, subjects will be given $30.00 for completed diary and for expenses related to study participation (parking, gas, and transportation).

Students and Employees over whom Key Personnel have a supervisory role may not be enrolled in this study.

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Subjects who are less than 18 years of age, those not currently legally able to make medical decisions or who are otherwise considered incompetent will not be approached for participation in this study.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

see #4

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant women, prisoners or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

Herbal products have been used relatively safe for years with very few adverse effects. FIDAPIN, a topical analgesic with similar essential oil components as Bonipar (except for one herbal oil), had been studied in a randomized double-blind placebo controlled trial in 196 subjects with chronic musculoskeletal pain involving Fidapin (n=64), Diclofenac ointment (n=67) and a placebo (Jasmine oil, n=65). All groups showed a significant decrease in pain after 2 and 4 weeks. Both the diclofenac (4 subjects) and placebo group (2 subjects) developed adverse events (superficial rashes) while those receiving Fidapin did not experience any adverse effects or complications. The superficial rashes receded after discontinuation of the therapy. One subject on the diclofenac group had a progressive radicular pain and paresthesia – that subsided when it was discontinued after 8 days of use. Another observation was that Fidapin had a relatively rapid onset of action.

Since Bonipar is a topical analgesic made from naturally-occurring essential oils, the risk of developing any systemic adverse effects is highly unlikely. There is a small possibility that some patients may develop

cutaneous reactions, e.g. rashes, skin irritation etc. If such reactions were to occur, the study would be immediately halted for that subject and treatment would be offered at no costs to the patient. All subjects will have a skin examination on the treated area at baseline (before treatment). The area will be examined for the presence of the following: skin discolorations, hyperemia, skin elevations, scratch marks, wheals, pruritus, bruises, hair pattern, skin effusions and presence of any abnormal skin characteristics. AEs, if any, will be recorded at the follow-up study visit and the patient may be asked to return if the PI deems it necessary.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There will be no additional costs as a result of being in this study. Bonipar and diclofenac topical solution 1.5% will be provided free of charge for use in this study.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

The primary objective of the study is to evaluate the reduction in acute and chronic musculoskeletal pain by Bonipar in comparison to conventional treatment of diclofenac topical solution 1.5%. Pain responses at base line and at two-week follow up will be measured in the scale of 0 to 10, where 0 indicates no pain and 10 indicates highest level of pain. For each patient, primary outcome variable will be measured in two ways: i) compute whether the decrease in pain by 50% between baseline and 1-week follow-up (i.e. binary variable) and, ii) calculate the absolute difference in pain score between baseline and 1-week follow-up (continuous variable). Statistical power and sample size was determined based on the binary outcome variable.

Initial data characteristics will be compared between groups using chi-square for categorical variables and t-test or Wilcoxon rank sum test for continuous variables. Change in pain from baseline will be compared between two treatment groups using chi-square test for binary variable and t-test or equivalent non-parametric test for continuous variable, as appropriate. The significance level of the test will be targeted at α=0.05 (one sided). Non-inferiority will be established, at the 0.05 significance level if the lower limit of equivalent two-sided 90% confidence interval for the difference in success rate is above non-inferiority margin. Multivariable linear regression analysis will be performed to examine the changes in pain score adjusting potential confounders such as type of pain (lumbar vs. other), prior duration with pain. Reports of side effects will also be investigated between two groups. As an exploratory analysis we will evaluate the time to onset of action between two topical drugs, where time to onset variable will be measured within 1 hour (as $\leq$ 15 min, < 30 min, $\leq$ 45 min or $\leq$ 60 min) after the application of drugs at clinic. No adjustments will be made for the multiple endpoints testing. All analyses will be conducted using SAS version 9.4.

Analysis will be performed for the full datasets and by pain group (acute and chronic).

Power Calculation:
Preliminary data to base on power analysis
Meta-analysis from Massey et al (Cochrane Database Syst Rev.; (6) 2014) presented data from combined three studies comparing topical diclofenac versus placebo (Joussellin 2003; Predel 2004; Rowbotham 2003). A total of 319 participants were treated with topical diclofenac, and 307 with placebo. The success rate (i.e. patient reported pain relief at least 50%) was
52% (166/319, range 39% to 92%) for group treated with diclofenac and 25% (77/307, range 8% to 36%) for placebo group.

Assumptions behind power calculations:

There will be two equal-sized treatment arms, one containing diclofenac topical solution 1.5% treated patients and the other Bonipar treated patients. The arms will be compared for a difference in success rate (i.e. pain reduction at least 50% from baseline to follow-up at 1 weeks) with Z-test (one-sided at alpha=0. 05) using PASS software. Two scenarios will be considered, as follows:

1. The success rate will be 52% among diclofenac topical solution 1.5%vs. 62% true success rate among Bonipar group (with -10% non-inferiority margin)
2. The success rate will be 52% among diclofenac topical solution 1.5%vs. 67% true success rate among Bonipar group (with -10% non-inferiority margin)

Difference $D_0=P_2- P_1$ (non-inferiority margin)

H_0: $P_2- P_1 \leq D_0$

H_1: $P_2- P_1 = D_1>D_0$

D_1: True observed difference i.e. $P_1(H_1) - P_2$

Where P_1 & P_2 represent the proportion of success for Bonipar and diclofenac topical solution 1.5% group respectively.

Statistical power and required sample size for the aforementioned two scenarios are presented in the table.

Power	Alpha	D_0	D_1	P_2	$P_1(H_0)$	$P_1(H_1)$	N1	N2	Total N
0.80	0.05	-0.10	0.10	0.52	0.42	0.62	76	76	152
0.80	0.05	-0.10	0.15	0.52	0.42	0.67	49	49	98

Pass software was used to determine sample size of the study. With a sample size of 152 (76 per group), we will be able to achieve 80% statistical power to detect a difference in success rate on pain reduction of 10% between Bonipar and diclofenac topical solution 1.5% groups with a non-inferiority margin of 10%. If we consider a 10% drop out rate, we will need to enroll 8 more patients per group a total of 168. This 10% drop out rate did not reflect the patient population. Consequently, we plan to consent 240 subjects in order to reach our target goal of 152 completed subjects.

Interim Analysis:
After approximately 50% of the study is completed (75 to 95 patients), we plan to carry a preliminary statistical analysis of the patients who have completed the study at that time.
We do NOT plan to analyze the primary data i.e. the pain scores of the two groups because that process could potentially interfere with the non-inferiority integrity of the final analysis of that data.

We are therefore proposing on the advice and approval of our Consultant Statisticians:
1) to analyze all the data as one group and not to differentiate between the group receiving the study drug and the group receiving Diclofenac.
2) to analyze the secondary data including adverse effects and dropout status from the study and to perform a comparative analysis between the two groups.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

There is no plan for formal data and safety monitoring board. Given the small target size for enrollment, we do not feel that a formal DSMB is necessary. However, all adverse events should be immediately reported to the principal investigator, Dr. Lance Roy. The principal investigator will report any adverse and serious adverse events to the IRB during the study. PI will review and sign off on all adverse events on a weekly basis. All adverse events will be reported to the FDA at the end of the study.