1. TITLE PAGE

STUDY TITLE	A Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Three-Arm, Multi-Site Study to Evaluate the Clinical Equivalence of Diclofenac Sodium Topical Gel 1% (Hi-Tech Pharmacal Co., Inc.) with Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% (Novartis) in Patients with Osteoarthritis of the Knee
SPONSOR	Hi-Tech Pharmacal Co., Inc. Address: 369 Bayview Avenue Amityville, NY, 11701, USA
PROTOCOL NUMBER	OGD protocol #P130021 assigned by the FDA in its April 16, 2015 letter
STUDY CLASSIFICATION	Bioequivalence Study with Clinical Endpoint
INVESTIGATIONAL PRODUCT	Test Product: Diclofenac Sodium Topical Gel 1% (Hi-Tech Pharmacal Co., Inc.) Reference Product: Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% (Novartis) Placebo: Topical gel (vehicle) with no active ingredient
INDICATION	Pain associated with osteoarthritis of knee
DOSE	Subjects were randomized to receive a 4 gram dose of the generic Diclofenac Sodium Topical Gel, 1% (Test), the Reference Listed Drug (RLD), or Placebo applied to the arthritic knee four times daily for eight (8) weeks.
STUDY POPULATION	All included subjects were at least 35 years of age, of either sex, of any race, were diagnosed with osteoarthritis of the knee in one or both knees and met all inclusion criteria and none of the exclusion criteria.
FIRST PATIENT TREATED	December 8, 2014

LAST PATIENT COMPLETED	April 01, 2016
SPONSORS RESPONSIBLE MEDICAL OFFICER	Biswajit Pati, Ph.D., Senior Vice President, Research & Development
SPONSOR REPRESENTATIVE	Biswajit Pati, Ph.D., Senior Vice President, Research & Development Responsibility: Sr. VP, Research and Development Akorn Pharmaceuticals, Inc. 1925 West Field Court, Suite 300, Lake Forest, IL 60045, USA Tel: 847-353-4966 Fax: 847-279-6191 Email: Biswajit.pati@akorn.com
DATE	June 21st, 2018

2. SYNOPSIS

NAME OF SPONSOR/COMPANY	Hi-Tech Pharmacal Co., Inc.
NAME OF FINISHED PRODUCT	Diclofenac Sodium Topical Gel 1%
NAME OF ACTIVE INGREDIENT	Diclofenac Sodium
STUDY TITLE	A Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Three-Arm, Multi-Site Study to Evaluate the Clinical Equivalence of Diclofenac Sodium Topical Gel 1% (Hi-Tech Pharmacal Co., Inc.) With Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% (Novartis) in Patients with Osteoarthritis of the Knee
INVESTIGATORS	The entire listing of all Investigators can be found in Appendices 16.1.4.1-16.1.4.6
STUDY CENTRES	55 centers in Ukraine, Poland, Romania, Lithuania, Latvia and Estonia
STUDY PERIOD	8 December 2014 (first patient in for the first protocol version) to 01 April 2016 (last patient out)
PHASE OF DEVELOPMENT	Bioequivalence Study with Clinical Endpoint
OBJECTIVES	The objectives of the study were to demonstrate efficacy and safety of Hi-Tech Pharmacal Co., Inc's Diclofenac Sodium Topical Gel 1% compared to Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% (Novartis) in the treatment of patients with osteoarthritis of the knee.
DESIGN	This study followed a double-blind, randomized, placebo-controlled, parallel group, three-arm, multi-site, 5-treatment visit study design with 934 subjects. Study centers (in several European countries) participated in this study to achieve approximately 800 modified Intention-to-Treat (ITT) patients, in order to complete at least 750 Per Protocol (PP) patients. Patients were randomized

1:1:1 to receive the Test Product, or the Reference Product, or Placebo treatment, respectively.

Patients with osteoarthritis (OA) of the knee were asked to administer the study medication four (4) times daily for eight (8) weeks. Patients visited the study site as per the following visit schedule:

Visit 0/Screening – Day -9±2
Visit 1/Baseline – Day 0
Visit 2/Week 2 – Day 14±2
Visit 3/Week 4 – Day 28±2
Visit 4/Week 6 – Day 42±2
Visit 5 – Day 56±2/Termination Visit

Visits were calculated based on Visit 1 Day 0. A window of ±2 days was allowed for each visit (other than Visit 1) however the total duration of study drug administration could not exceed 8 weeks ±2 days.

The initial protocol versions prior to the protocol version 1.9 had the following study schedule to accommodate the placebo run-in during the pain medication washout period (between Visits 0 and 1):

Visit -1/Prescreening – Day -30 to -10
Visit 0/Screening – Day -7
Visit 1/Baseline – Day 0
Visit 2/Week 2 – Day 14±2
Visit 3/Week 4 – Day 28±2
Visit 4/Week 6 – Day 42±2
Visit 5/Week 8 – Day 56±2

In its April 16, 2015 response to our protocol DICL001 (its initial version 1.5 was submitted to the FDA OGD on September 24, 2013), the OGD disagreed with our proposed use of placebo gel during the pain medication washout period and hence the protocol was modified accordingly.

SAMPLE SIZE, PLANNED AND ANALYZED	Planned: 900 subjects in total with 300 subjects in each treatment group Analyzed: 934 subjects in total with 316 subjects who received Test Product, 312 Reference Product and 306 Placebo Enrolled: 934 Screened: 1039
INDICATION	Pain associated with osteoarthritis of knee
MAIN CRITERIA FOR INCLUSION (PROTOCOL VERSION 1.9)*	1. Ambulatory male and non-pregnant females 35 years and older diagnosed with osteoarthritis according to the American College of Rheumatology Criteria (ACR) in one knee. Target knee is the one with higher level of pain. ACR Criteria includes: Knee Pain and at least 3 of the following: 1) age $\geq$ 50 2) stiffness lasting < 30 mins 3) bony tenderness 4) crepitus 5) bony enlargement 6) no palpable warmth 2. Symptom onset of > 6 Months prior to Screening for the target knee. 3. If female and of child-bearing potential, prepare to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., IUD, oral, transdermal, injected, implanted hormonal contraceptives or condom + spermicide). 4. Periarticular knee pain due to osteoarthritis (not bursitis, tendonitis etc.) that required the use of oral or topical treatments (e.g., NSAIDs or acetaminophen). 5. Radiograph of the target knee within the previous year with a Grade 1, 2 or 3 disease based upon the Kellgren-Lawrence disease severity scale. 6. After a minimum of 7-day wash out of all pain medication has

	Baseline pain on movement score of ≥ 50mm on a 0-100-mm Visual Analogue Scale for the target knee. 7. After a minimum of 7-day wash out of all pain medication has Baseline WOMAC Pain sub scale of ≥ 9 on a 5 question, 5 point (0 to 4) Likert scale for the target knee. 8. Willing and able to use only acetaminophen as rescue medication. 9. Willing and able to comply with the study requirements.
MAIN CRITERIA FOR EXCLUSION (PROTOCOL VERSION 1.9)*	1. Females who are pregnant, breast feeding, or planning a pregnancy. 2. Radiograph of the target knee within the previous year with a Grade 4 score on the Kellgren-Lawrence disease severity scale. 3. History of osteoarthritis in the contralateral knee requiring medication (OTC or prescription) within 12 months of screening. 4. After a minimum of 7-day wash out of all pain medication has Baseline pain on movement score of ≥ 20mm on a 0-100-mm Visual Analogue Scale for the contralateral knee immediately prior to randomization. 5. Known history of secondary osteoarthritis (e.g. congenital, traumatic, gouty arthritis) of the knee or rheumatoid arthritis. 6. Known history of other chronic inflammatory diseases, (e.g., colitis) or fibromyalgia during last 5 years. Patients whose disease was diagnosed at least 5 (five) years prior to screening visit and have had no known disease activity (i.e., neither disease related complaints nor disease treatment prescribed) since then may enter in the study. 7. History of asthma, hypertension, myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function or liver disease. Patients who have had high blood pressure measured at least 2 (two) years prior to screening visit and have had no disease activity (i.e., no record of hypertension or anti-hypertensive treatment prescribed) for at least 2 (two) years prior to

screening visit may enter in the study.

8. History of coronary artery bypass graft within 6 months of screening.

9. Concomitant acetylsalicylic acid therapy other than a stable low dose used for cardiac prophylaxis (max. 162 mg daily) taken for at least 3 months prior to enrollment and maintained throughout the duration of the study.

10. Use of warfarin or other anticoagulant therapy within 30 days of screening.

11. Use of ACE inhibitors, cyclosporine, diuretics, lithium or methotrexate, within 30 days of screening or during the study.

12. Known history of gastrointestinal bleeding or peptic ulcer disease.

13. Abnormal screening clinical laboratory evaluations which the Investigator deems clinically significant.

14. Known allergy to aspirin or NSAIDs.

15. Skin lesions or wounds in the affected area.

16. Significant (requiring surgery) injury or major knee surgery to either knee within six months prior to screening.

17. Transaminase levels that are more than two times the upper limit of the normal range at screening.

18. Any other acute or chronic illness that in the opinion of the investigator could compromise the integrity of study data or place the Patient at risk by participating in the study.

19. Concomitant use of corticosteroids (any formulation) or use within 30 days of study randomization.

20. Receipt of any drug as part of a research study within 30 days prior to screening.

21. Previous randomization into this study.

22. Known allergy (hypersensitivity) to acetaminophen.

* - the inclusion and exclusion criteria of the earlier protocol versions are in the DICL001 protocols file and Chapter 9.8 of this

	CSR.
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION	Investigational drug (Test Product): Diclofenac Sodium Topical Gel 1% (Hi-Tech Pharmacal Co., Inc.) Dosage and regimen: Test Drug was used on knees to treat arthritis pain and was administered topically. Subjects applied 4 grams for 4 times a day (total dose for one day was 16 grams). All subjects received medication from the following batches: 620576 (Diclofenac Sodium Topical Gel) W3633 or W4347 (Voltaren® Gel) 624354 (Placebo)
REFERENCE PRODUCT; DOSE AND MODE OF ADMINISTRATION	Reference Product: Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% (Novartis) Placebo: Topical gel (vehicle) with no active ingredient Dosage and regimen: Reference Drug and Placebo were used on knees to treat arthritis pain and were administered topically. Subjects applied 4 grams four times a day (total dose for one day was 16 grams). All subjects received medication from the following batches: 620576 (Diclofenac Sodium Topical Gel) W3633 or W4347 (Voltaren® Gel) 624354 (Placebo)
DURATION OF STUDY FOR INDIVIDUAL SUBJECT	8 weeks ±2 days
CRITERIA FOR EVALUATION	Criteria for Effectiveness: Bioequivalence for Test Drug is established if with 90% confidence the ratio of means of the WOMAC Pain scores for Test and RLD remains within 0.80 and 1.25. The sensitivity of the study will be acceptable if mean changes from Baseline in the WOMAC Pain scores for Test and RLD are statistically significantly greater ($p<0.05$) than that for the Placebo in the ANCOVA based on the

Treatment and Placebo results.

Safety Measures:

Safety measures will include the incidences of treatment emergent adverse events (reported, elicited and observed), abnormal vital signs, clinically significant changes from Baseline in physical examination results.

STATISTICAL METHODS

For efficacy data:

- Descriptive evaluation of all endpoints
- Ratio of mean WOMAC Pain scores between Test and Reference Products and their 90% confidence interval.
- Parametric method (ANCOVA) for the comparison of Treatment versus Placebo in the mean change from Baseline in the WOMAC Pain score

For safety evaluation:

- Descriptive statistical methods

ENDPOINTS

Primary Efficacy Endpoints

- Mean Change from Baseline to Week 8 in WOMAC Pain Scale

Secondary Efficacy Endpoints

- Superiority of Test and Reference against Placebo in the Mean Change from Baseline to Week 8 in the total WOMAC Pain score.

Safety Endpoints

- Incidences of treatment emergent adverse events
- Abnormal vital signs
- Clinically significant changes from Baseline in physical examination results.