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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Safety of a Diclofenac Sodium 75 mg/1 mL Solution (Akis®/Dicloin®) Administered as a Single Intravenous Bolus Injection in Healthy Men and Women

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Abstract

Background A 1-mL aqueous solution for parenteral injection containing diclofenac sodium and hydroxypropyl-β-cyclodextrin, presently on the market for intramuscular and subcutaneous administration (Akis®/Dicloin®), was further developed for intravenous (i.v.) bolus administration.

Objectives The study objective was to compare the tolerability and diclofenac pharmacokinetics after a single i.v. bolus of the investigational solution to those of other parenteral diclofenac products.

Methods The study comprised three parts: (i) Part 1: an exploratory dose-escalation study to evaluate the tolerability of 25 mg/1 mL, 50 mg/1 mL and 75 mg/1 mL diclofenac sodium formulations administered as a single 5-s i.v. bolus; (ii) Part 2: an exploratory, randomised, crossover study to evaluate the pharmacokinetics of diclofenac following 5-, 15-, and 30-s i.v. bolus injections of diclofenac sodium 75 mg/1 mL; (iii) Part 3: a randomised crossover study to compare the pharmacokinetics of diclofenac following a 5-s i.v. bolus of the 75 mg/1 mL solution to the pharmacokinetics of diclofenac following a 30-min i.v. infusion or intramuscular administration of a 75 mg/3 mL reference formulation.

Results The extent of exposure to diclofenac sodium afforded by the 5-s i.v. bolus of 75 mg/1 mL was equivalent to that provided by the 30-min i.v. infusion of 75 mg/3 mL, since the 90% confidence interval of the geometric mean ratio (GMR) of the area under the curve (AUC) from time 0 to the last plasma concentration time t ($AUC_{0\text{-}t}$) was within the limits 80.00–125.00%, as was the 90% confidence interval of the GMR of the AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$). The maximum observed plasma concentration (C_{max}) was approximately 2.7-fold higher and was achieved earlier (0.05 vs. 0.50 h) with the 1 mL than with the 3 mL formulation, and was similar to data published for a 75 mg/2 mL formulation given as a 15-s i.v. bolus.

Conclusions Diclofenac sodium 75 mg/1 mL solution administered as a 5-s i.v. bolus was well tolerated. The pharmacokinetic profile, which showed a faster onset and a higher concentration peak than seen for other products and administration routes, suggests a superior analgesic effect.

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Key Points

When administered to healthy volunteers as a 5-s i.v. bolus, the Akis®/Dicloin® 75 mg/1 mL solution for injection was safe and well tolerated.

The observed pharmacokinetic profile indicates a more rapid onset and a higher concentration peak as compared to those of other marketed parenteral formulations and administration routes, suggesting a superior analgesic effect.

1 Introduction

Diclofenac is a well-known nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory activities [1, 2] that is most often administered orally, but also topically, intravenously (i.v.), intramuscularly (i.m.), subcutaneously (s.c.), intracolonically and rectally [2, 3]. Parenteral administration is often preferred when patients cannot tolerate or are unable to take oral medications and/or require rapid onset of analgesia.

Ready-to-use parenteral prefilled syringe formulations containing diclofenac sodium and hydroxypropyl-β-cyclodextrin (HPβCD) as a complexing agent in 1 mL of water for injection (Akis®/Dicloin®, IBSA Institut Biochimique S.A.) are presently available on the market at three different strengths: 25 mg/mL, 50 mg/mL and 75 mg/mL. These formulations are approved for the short-term treatment of acute forms of pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and postoperative pain [4]. Importantly, these small-volume formulations allow diclofenac to be administered both intramuscularly and subcutaneously, the latter route offering some advantages over the former, such as ease of use, better tolerability, and potentially safer administration in patients with reduced muscular mass due to prolonged inactivity or ageing. The availability of a ready-to-use form at three different strengths should further simplify the approach used by physicians: employ the lowest dose necessary to control symptoms, adapt the level of analgesia to the specific need of each patient, and eventually minimise undesirable effects [4].

The possibility of further extending the administration options for the same formulation to include i.v. bolus injection is particularly interesting in view of its possible use in the hospital setting, e.g. for perioperative pain management, alone or in combination with other drugs, according to the current concepts of multimodal therapy, which have established themselves due to the increasing evidence of their ability to minimise pain and accelerate patient recovery and discharge [5, 6]. Following scientific advice from the UK Medicines and Healthcare Products Regulatory Agency (MHRA), the present study was designed taking into consideration the applicable regulatory document on bioequivalence studies [7] as well as the most relevant published data on the reference diclofenac-containing parenteral products [8, 9]. The aim of the study was to evaluate the pharmacokinetic profile of the test diclofenac sodium 1-mL prefilled syringe formulation (Akis®/Dicloin®) administered as a single i.v. bolus, and then compare it to those of other parenteral formulations. The reference product administered during the study and directly compared with Akis®/Dicloin® is Voltarol® 75 mg/3 mL (diclofenac sodium; Novartis Pharmaceuticals UK Ltd) [8], which is authorised for intramuscular administration and i.v. infusion and, unlike the test product, does not contain HPβCD as a complexing agent.

2 Methods

2.1 Study Design and Procedures

The study was designed according to the EMA guideline for bioequivalence studies [7].

The study protocol (no. 14CH/DCiv11) was approved by the Ethics Committee of Canton Ticino, Switzerland and the Swiss Federal Health Authorities, and was performed in accordance with the Declaration of Helsinki and harmonised European standards for GCP (ICH E6 1.24). All subjects were given a detailed description of the study and all of them gave written informed consent before enrolment. The clinical phase of the study was conducted between April and November 2015.

The test investigational product was a diclofenac sodium solution for injection in a prefilled syringe at concentrations of 25 mg/1 mL, 50 mg/1 mL and 75 mg/1 mL (Akis®/Dicloin®) [4].

The study included the following three parts:

Part 1. This exploratory study was designed to evaluate the safety and tolerability of a single dose of each strength of the investigational product (i.e. 25 mg, 50 mg or 75 mg in 1 mL of solution for injection) administered by i.v. bolus at a 5-s injection rate according to a three-cohort dose-escalation design. Subsequent cohorts were treated only after a full safety assessment of the previous cohort. If no safety issues were observed, the study could proceed with the next part of the study.

Part 2. This exploratory study was designed to evaluate the pharmacokinetic profile of diclofenac following i.v. bolus injection of the test diclofenac sodium 75 mg/1 mL solution at three different injection rates, i.e., 5-, 15- and 30-s, according to an open-label, randomised, crossover design. The safety and tolerability of the investigational product were also evaluated. Pharmacokinetic and safety results were taken into consideration to determine the injection rate used in part 3 of the study.

Part 3. This open-label, randomised, crossover study was designed to compare the extent of exposure to diclofenac attained with the test diclofenac sodium 75 mg/1 mL solution administered as a single i.v. bolus at the 5-s injection rate to the extent of exposure obtained with the reference diclofenac sodium 75 mg/3 mL solution (Voltarol®) [8] administered by either i.m. injection or as a 30-min i.v. infusion.

A washout interval of at least 7 days separated subsequent administrations in parts 2 and 3 of the study. This washout interval was considered adequate to ensure that drug

concentrations were below the lower limit of bioanalytical diclofenac quantification pre-dose in subsequent periods, considering that the half-life of diclofenac is approximately 2 h [4, 8].

The study randomisation lists for parts 2 and 3 of the study were generated using the PLAN procedure of the software SAS/STAT® version 9.3.

During each study period, the subjects were confined to the clinical centre from the evening preceding investigational product administration until 8 h post-dose. Water was allowed as desired, except for 1 h before and 1 h after administration. Investigational products were administered under fasting conditions and a standardised lunch was served at approximately 5 h post-dose. One cup of coffee or tea and one cigarette were allowed after each meal only.

2.2 Subjects

Healthy male and female volunteers aged 18–53 years with a body mass index of 19.0–30.0 kg/m^2 were enrolled in the study. All volunteers were in good physical health, as assessed through a full physical examination, electrocardiogram (ECG) recording, vital signs measurements and clinical laboratory assays, according to the study inclusion criteria. No subjects were on abnormal diets or had a history of drug, alcohol, caffeine or tobacco abuse. Exclusion criteria included a history or the presence of significant renal, hepatic, gastrointestinal (in particular active or suspected gastrointestinal ulcers or bleeding), genitourinary, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that could interfere with the aim of the study; a history of haemorrhagic diathesis, thalassemia, sickle-cell disease, glucose-6-phosphate dehydrogenase deficiency or any other condition that could potentially lead to haemolysis; or a history of hypersensitivity or allergic reactions to the active principle, to formulation ingredients and/or to other NSAIDs. Medications, including over-the-counter medications and herbal products, were not allowed for 2 weeks before the study. In particular, NSAIDs and anticoagulants were not allowed for 2 weeks before screening and during the entire study. Hormonal contraceptives for females were allowed. Subjects were not enrolled if they had participated in other clinical trials or donated blood in the past 3 months.

2.3 Blood Sampling

Sampling time points were selected based on previously reported data [10]. During each period of parts 2 and 3 of the study, venous blood samples (8 mL) for diclofenac determination were collected from a forearm vein at pre-dose (0), 3, 6, 10, 20, 30, 40, 50 min, 1, 1.25, 1.5, 2, 3, 4, 6 and 8 h post-dose. For the infusions, the dosing time (0 h) was set at the start of infusion. Blood samples for pharmacokinetic analysis were collected using an indwelling catheter with a switch valve. Samplings were performed from the arm not used for injection/infusion. After each sampling, the cannula was rinsed with about 1 mL of sterile saline solution containing 20 IU/mL Na-heparin. At each collection time, the first 2 mL of blood were discarded to avoid contaminating the sample with heparin. The remaining 6 mL were collected from the catheter and transferred with a syringe into heparinised tubes (Na-heparin).

The samples were stored on ice for a maximum of 20 min and then centrifuged at 4° C for 10 min at $2500 \times g$ to obtain plasma. Each plasma sample was immediately transferred into pre-labelled polypropylene tubes and stored frozen at ≤ -20° C until analyses.

2.4 Bioanalytical Assay

Concentrations of diclofenac in plasma were determined by a blinded analyst at Nuvisan GmbH (Germany) using a LC–MS/MS method developed and validated according to the requirements of the EMA and FDA guidance documents on bioanalytical method validation [11, 12]. The method had a lower quantification limit (LQL) of 10.0 ng/mL and an upper quantification limit (UQL) of 30,000 ng/mL and adhered to the regulatory requirements for selectivity, sensitivity, precision, accuracy, recovery, carryover, matrix effect and stability.

Internal standards for the analysis were the deuterated form of the analyte (diclofenac-D_4).

Diclofenac calibration standards in the range of 10–30,000 ng/mL and QC samples at the levels LQL (10.0 ng/mL), low (30.0 ng/mL), medium 1 (1000 ng/mL), medium 2 (15,000 ng/mL) and high (22,500 ng/mL) were prepared freshly in human plasma, pipetted into appropriately labelled tubes, and stored in a freezer at -20 °C ± 5 °C just before the start of analysis. The retention time, peak area and peak height of the analyte and internal standard were determined using the Analyst 1.6.2 integration system. Analyte concentrations were evaluated using the internal standard method. The standard curves were calculated from the peak area ratio (p.a.r.) of analyte to internal standard and the nominal diclofenac concentrations using linear regression: $y = a + bx$ with $1/x^2$ weighting. The measured peak area ratios of the subject and QC samples were converted into concentrations using the following equation: concentration = (p.a.r $- a$)/b.

2.5 Pharmacokinetic Parameters

The following pharmacokinetic parameters were determined or calculated via noncompartmental analysis using the validated software Phoenix WinNonLin® 6.3 (Certara, Inc.):

maximum observed plasma concentration of diclofenac (C_{max}), time to C_{max} (t_{max}), and the areas under the concentration–time curve up to the last observed concentration time t ($AUC_{0\text{-}t}$) and extrapolated to infinity ($AUC_{0\text{-}\infty}$), as calculated using the linear trapezoidal rule.

The half-life of diclofenac in plasma ($t_{½}$) and the theoretical plasma concentration of diclofenac at $t = 0$ for the i.v. bolus (C_0) were also calculated. Since the first two sampling points (i.e. 3 and 6 min) were sufficiently near the dosing time ($t = 0$), back-extrapolation from the first two concentration values gave a reasonable estimation of the initial concentration C_0.

In addition, the mean C_{max} value for the test 75 mg/1 mL product administered by a 5-s i.v. bolus injection was calculated using C_{max} data from parts 2 and 3 of the study.

2.6 Safety

The safety profile of the investigational products was assessed in each study part by evaluating treatment-emergent adverse events, physical examination, electrocardiogram (ECG), routine laboratory tests, and vital sign checks. Vital signs (blood pressure and heart rate) were measured at screening, in the evening of the day before administration and at 8 h post-dose. A 12-lead resting ECG was recorded at screening, 2 h post-dose, and at the final visit. Blood and urine samples were collected for routine haematology, blood chemistry, virology and urinalysis at screening and the final visit. Adverse events were assessed throughout the study up to follow-up (4 days after the treatment day), and were coded using MedDRA® version 18.1. A full physical examination was performed by the investigator at screening and at the final visit.

In each part of the study, the occurrence of thrombophlebitis at the i.v. injection and infusion sites was assessed at baseline, 4 and 8 h post-dose, at the final visit and at the follow-up using the visual infusion phlebitis scale [13], which ranges from a score of 0 (no sign of phlebitis) to a score of 5 (advanced thrombophlebitis).

2.7 Sample Size

Overall, 35 subjects were included in the study, as follows:

Part 1. Three (3) healthy male and female subjects per cohort (9 subjects in total) were included. This sample size, not based on any formal calculation, was deemed sufficient for the exploratory evaluation of the safety and tolerability profile of the test product at the three different doses.

Part 2. Eight (8) healthy male and female subjects were included according to the randomization list and crossover design. This sample size was deemed sufficient for the exploratory purposes of this part of the study.

Part 3. According to the current European Bioequivalence Guideline [7], at least 12 subjects were to be enrolled in order to obtain a reliable statistical comparison between investigational products. The sample size was increased to 18 in order to have at least 12 evaluable subjects in case of withdrawal.

2.8 Statistical Analyses

The statistical analyses were performed using SAS® software version 9.3 (TS1M1) for Windows® and Phoenix WinNonLin® 6.3, Certara Inc.

For all parts of the study, data were summarised by descriptive statistics.

For part 3 of the study, log-transformed $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ data were compared between the test investigational product (diclofenac sodium 75 mg/1 mL) administered by 5-s i.v. bolus injection and the reference diclofenac sodium 75 mg/3 mL product (Voltarol®) administered by i.m. injection or by 30-min i.v. infusion, using a classical bioequivalence test [7]. The analysis for each comparison was conducted after excluding the data from the treatment that was not relevant for the comparison. The statistical analysis took into account treatment, period, sequence, and subject within sequence as fixed effects. The similarity criteria were a geometric mean ratio (GMR) for the parameter under consideration of approximately 100% as well as a 90% confidence interval (CI) for this ratio within the 80.00–125.00% range.

The mean C_{max} value for the test diclofenac sodium 75 mg/1 mL product, as calculated from C_{max} data obtained in parts 2 and 3 of the study, was descriptively compared with literature data for diclofenac sodium 75 mg/2 mL solution (Dyloject®, Javelin Pharmaceuticals UK Ltd), which was approved for i.v. bolus injection [9, 10] and later withdrawn from the market due to problems linked to the manufacturing process [14]. Before the comparison, the precision level of the mean C_{max} was assessed and defined adequate if the distance between the mean C_{max} value and its 90% confidence interval limits was $\leq 20\%$ of the mean value.

3 Results

3.1 Subjects

Overall, 35 subjects were enrolled in the study as planned: 9 in part 1, 8 in part 2, and 18 in part 3 of the study. All of them received the study treatments, completed the study per protocol, and were included in the analysis. Demographic characteristics of the analysed subjects are presented in Table 1. All 35 enrolled subjects satisfied the study inclusion criteria. All subjects were in good physical and mental

health, as determined on the basis of medical and surgical history and physical examination. One woman was postmenopausal for at least 1 year and all the other women used reliable contraceptive methods. No subject was taking any previous medication at study entry, except for three women on oral contraceptives.

3.2 Safety

All tested treatments showed a good safety profile, and no subject withdrew from the study due to an adverse event. No signs of thrombophlebitis were observed following either i.v. bolus or i.v. infusion administration, and no significant effects on laboratory parameters, vital signs, body weight or ECG were observed.

Part 1. No treatment-emergent adverse events occurred during this part of the study with any of the doses of the investigational product.

Part 2. Two treatment-emergent adverse events, both consisting of left arm discomfort, were reported by one subject at the 15-s and 30-s injection rates of the test investigational product. The two events were of mild intensity, lasted for 2 min each, and were deemed to be probably related to study treatment.

Part 3. Headache of moderate intensity was reported by one subject approximately 6 days after investigational product administration. The event was not related to treatment.

Table 1 Demographic data of study subjects (all parts of the study; $N = 35$)

Characteristic	Value
Sex	
Females	17 (48.6%)
Males	18 (51.4%)
Age (years)	
Mean ± SD	41.1 ± 9.9
Range	19–53
Body weight (kg)	
Mean ± SD	67.52 ± 11.34
Range	46.3 – 92.0
Height (cm)	
Mean ± SD	167.8 ± 7.6
Range	146–183
BMI (kg/m^2)	
Mean ± SD	23.89 ± 3.02
Range	19.0–30.0
Race	
White	35 (100.0%)

BMI body mass index, *SD* standard deviation

3.3 Pharmacokinetics

Part 2. The pharmacokinetic parameters of diclofenac sodium 75 mg/1 mL administered as an i.v. bolus at the three injection rates (5-, 15- and 30-s) were very similar (Table 2), with superimposable curves for the three treatments (Fig. 1). This indicated that the injection rate did not have any effect on the maximum observed plasma concentration of diclofenac (C_{max}), the extrapolated concentration at dosing (C_0), the half-life ($t_{½}$) and the extent of exposure (AUC). The fastest (5-s) injection rate was selected for further evaluation in the subsequent part of the study.

Part 3. The mean ± SD diclofenac plasma concentration–time profiles up to 2 h after administration of the test product (given as a 5-s i.v. bolus) and of the reference product (given by i.m. injection or as a 30-min infusion) are shown in Fig. 2. The main plasma pharmacokinetic parameters (mean ± SD) are presented in Table 3.

Consistent with the differences between administering a rapid 5-s i.v. bolus versus a 30-min infusion, the observed C_{max} was on average approximately 2.7-fold higher and occurred earlier (i.e. 0.05 vs. 0.50 h) with the test product than with the reference product Voltarol®. The half-lives for

Table 2 Diclofenac pharmacokinetic parameters after single administration of the test diclofenac sodium 75 mg/1 mL solution administered by 5-, 15- and 30-s i.v. bolus injection (part 2 of the study; $N = 8$)

Pharmacokinetic parameter	Test diclofenac sodium 75 mg/1 mL solution		
	5-s i.v. bolus	15-s i.v. bolus	30-s i.v. bolus
C_0 (ng/mL), mean ± SD	28,001.33 ± 6857.41	26,481.69 ± 5598.40	27,107.16 ± 8279.07
C_{max} (ng/mL), mean ± SD	17,712.50 ± 3315.95	17,587.50 ± 3461.81	17,987.50 ± 3558.67
t_{max} (h), median (range)	0.05 (0.05–0.05)	0.05 (0.05–0.05)	0.05 (0.05–0.05)
AUC_{0-t} (ng·h/mL), mean ± SD	5383.81 ± 1020.31	5203.95 ± 1113.13	5557.90 ± 1041.00
$AUC_{0-\infty}$ (ng·h/mL), mean ± SD	5409.80 ± 1017.54	5235.01 ± 1108.17	5582.57 ± 1039.01
$t_{½}$ (h), mean ± SD	1.30 ± 0.29	1.27 ± 0.22	1.46 ± 0.20

AUC_{0-t} area under the concentration–time curve from time 0 to the last observed concentration time t, $AUC_{0-\infty}$ area under the concentration–time curve from time 0 to infinity, C_0 theoretical plasma concentration at $t = 0$, C_{max} maximum plasma concentration, *i.v.* intravenous, *SD* standard deviation, $t_{½}$ terminal half-life, t_{max} time to achieve C_{max}

the two treatments were very similar, with mean values of 1.47 ± 0.32 and 1.37 ± 0.34 h. This rapid elimination of the drug from the central compartment produced, as expected, a slightly higher diclofenac bioavailability after the more rapid i.v. bolus than the slow i.v. infusion. Consequently, the test/reference ratios of the geometric means (GMR %) for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were 112.69% and 112.65%, respectively. Despite these values, the two products were equivalent in terms of diclofenac exposure, because the 90% confidence intervals for the $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ geometric mean ratios were well within the acceptance limits of 80.00–125.00% (Table 4).

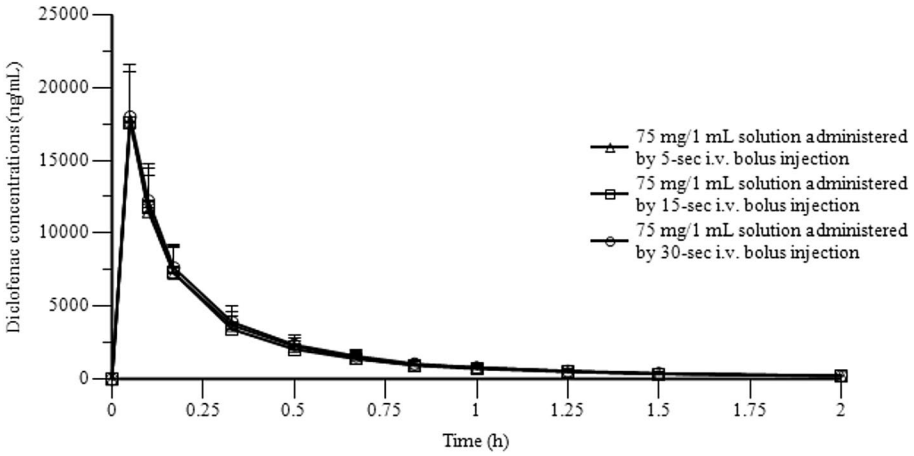

Fig. 1 Mean (+SD) plasma diclofenac concentration (ng/mL) vs. time profiles after single administration of the test diclofenac sodium 75 mg/1 mL solution administered by 5-, 15- and 30-s intravenous (i.v.) bolus injection. Linear scale. Part 2 of the study; $N = 8$

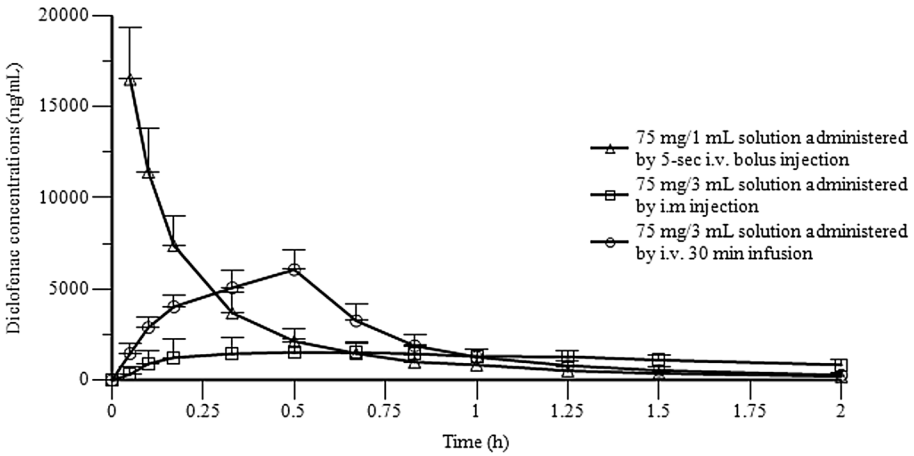

Fig. 2 Mean (+SD) plasma diclofenac concentration (ng/mL) vs. time profiles after single administration of the test diclofenac sodium 75 mg/1 mL solution administered by 5-s intravenous (i.v.) bolus injection and the reference 75 mg/3 mL solution administered by i.m injection and by 30 min i.v. infusion. Linear scale. Part 3 of the study; $N = 18$

Table 3 Pharmacokinetic parameters of diclofenac after single administration of the test diclofenac sodium 75 mg/1 mL solution administered by 5-s i.v. bolus injection and the reference 75 mg/3 mL solution administered by i.m injection or by 30 min i.v. infusion (part 3 of the study; $N = 18$)

Pharmacokinetic parameter	Test diclofenac sodium 75 mg/1 mL solution	Reference diclofenac sodium 75 mg/3 mL solution	
	5-s i.v. bolus	i.m. injection	30-min i.v. infusion
C_0 (ng/mL), mean ± SD	24,042.89 ± 4441.85	–	–
C_{max} (ng/mL), mean ± SD	16,505.56 ± 2829.77	1821.06 ± 825.98	6117.78 ± 1051.79
t_{max} (h), median (range)	0.05 (0.05–0.05)	0.67 (0.10–1.25)	0.50 (0.33–0.50)
$AUC_{0\text{-}t}$ (ng·h/mL), mean ± SD	5193.46 ± 1285.53	4117.29 ± 936.42	4584.13 ± 1014.20
$AUC_{0\text{-}\infty}$ (ng·h/mL), mean ± SD	5233.37 ± 1292.31	4319.59 ± 1009.99	4620.98 ± 1019.66
$t_{½}$ (h), mean ± SD	1.47 ± 0.32	1.82 ± 0.30	1.37 ± 0.34

$AUC_{0\text{-}t}$ area under the concentration–time curve from time 0 to the last observed concentration time t, $AUC_{0\text{-}\infty}$ area under the concentration–time curve from time 0 to infinity, C_0 theoretical plasma concentration at $t = 0$, C_{max} maximum plasma concentration, *i.v.* intravenous, *SD* standard deviation, $t_{½}$ terminal half-life, t_{max} time to achieve C_{max}

The pharmacokinetic profiles of the test product administered as an i.v. bolus and the reference product administered by i.m. injection were very dissimilar, as expected considering that an intravascular and an extravascular administration route were compared. While the half-life remained constant, with mean values of 1.47 ± 0.32 and 1.82 ± 0.30 h for the two investigational products, the mean diclofenac bioavailability following i.m. administration of the reference product was lower than for the test product administered as an i.v. bolus, as indicated by the test/reference geometric mean ratios (GMR %) of 120.76% and 125.58% for $AUC_{0\text{-}\infty}$ and $AUC_{0\text{-}t}$, respectively. Diclofenac exposure for the two treatments was similar in terms of $AUC_{0\text{-}\infty}$, as demonstrated by the 90% confidence interval, which was within the acceptance limits of 80.00–125.00%, but not in terms of $AUC_{0\text{-}t}$, since for this parameter the upper value of the 90% confidence interval overlapped the 125.00% limit.

C_{max} data comparison. The distance between the mean C_{max} value calculated using data from parts 2 and 3 of the study and the lower and upper limits of the 90% confidence interval was 996.38, i.e. below the 20% of the mean C_{max} value (delta: 3357.38). The precision level was considered adequate according to the study plan and sufficient for the planned comparison with literature data. Descriptive comparison results show that the mean C_{max} value observed in the present study with Akis®/Dicloin® 75 mg/1 mL solution administered as a single 5-s i.v. bolus (i.e. $16{,}876.92 \pm 2974.33$ ng/mL) was very similar to the mean C_{max} value reported in the literature for Dyloject® after an i.v. bolus of 15-s (i.e. $15{,}147 \pm 2829$ ng/mL) [9, 10]. In addition, the observed maximum plasma concentration was obtained, as expected, at the first post-dose assessment time (i.e. 0.05 h) for both products.

Table 4 Statistical analysis results after single administration of the test diclofenac sodium 75 mg/1 mL solution administered by a 5-s i.v. bolus injection and the reference 75 mg/3 mL solution administered by i.m. injection or by 30-min i.v. infusion (part 3 of the study; $N = 18$)

Treatment comparison	Pharmacokinetic parameter	GMR (%)	90% CI
Test 5-s i.v. bolus vs. Reference 30-min i.v. infusion	$AUC_{0\text{-}t}$	112.69	108.32–117.24%
	$AUC_{0\text{-}\infty}$	112.65	108.21–117.27%
Test 5-s i.v. bolus vs. Reference i.m. injection	$AUC_{0\text{-}t}$	125.58	122.14–129.12%
	$AUC_{0\text{-}\infty}$	120.76	117.87–123.73%

CI confidence interval, *GMR* geometric mean ratio, *i.v.* intravenous

4 Discussion

The present study was conducted as part of a clinical development programme to support the regulatory approval of the i.v. bolus route for Akis®/Dicloin®, a 25-mg, 50-mg and 75-mg diclofenac sodium-containing small-volume (1-mL) watery solution for injection (it is already licenced for i.m. and s.c. administration).

According to the design and aims of this study, which included three parts that were agreed with the MHRA, the general safety and local tolerability at the site of injection were investigated and an optimum injection rate for the test product was defined before conducting the bioavailability comparison.

Part 1, an exploratory study performed in 9 healthy volunteers (3 subjects/dose group), confirmed the safety of the three doses of the test product, i.e. 25 mg, 50 mg and 75 mg, administered as a single 1-mL i.v. bolus at an injection rate of 5-s. The highest dose of 75 mg was selected for parts 2 and 3 of the study, since this is the dose administered by i.v. infusion in common clinical practice.

In the 8 healthy volunteers enrolled in the subsequent exploratory study (denoted part 2) who randomly received the study treatments according to a crossover design, the pharmacokinetic parameters of the test 75 mg/1 mL product administered as an i.v. bolus at the three injection rates of 5-, 15- and 30-s were very similar. The superimposable curves for the three treatments indicated that the injection rate did not have any effect on the maximum observed plasma concentration of diclofenac (C_{max}) and the extent of exposure (AUC). The fastest (5-s) injection rate was selected for the comparative bioavailability assessment.

Part 3 of the study demonstrated that the test formulation administered as a 5-s i.v. bolus and the reference solution administered as a 30-min infusion, both containing 75 mg diclofenac sodium, were equivalent in terms of diclofenac exposure, as demonstrated by the 90% confidence intervals of the $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ geometric mean ratios, which were well within the acceptance limits of 80.00–125.00%. On the other hand, and as expected considering the fast i.v. bolus for the administration of the test product as compared to the extended infusion time for the reference solution, the observed C_{max} was higher and T_{max} occurred earlier for the test than for the reference product. Despite the higher C_{max}, however, there was no evidence of any increased safety risk, as only two minor adverse reactions—limb discomfort of mild intensity, resolved after a couple of minutes—occurred in two subjects (5.7%) following administration of the test product, no signs of thrombophlebitis were observed, and no significant effects of the test treatment on laboratory parameters, vital signs, body weight or ECG were reported. These findings are consistent with the results previously published

for a similar diclofenac sodium 75 mg/2 mL parenteral formulation (Dyloject®, Javelin Pharmaceuticals UK Ltd), also administered by i.v. bolus to patients receiving a single dose for the treatment of moderate or severe postsurgical dental pain [10, 15, 16]. Indeed, the safety profile of Dyloject® administered as a 15-s i.v. bolus was similar to that of the widely used 75 mg/3 mL diclofenac sodium formulation given by i.v. infusion, but with a significantly lower incidence of thrombophlebitis [10, 17].

Additionally, the diclofenac extent of exposure levels after the test i.v. bolus and the reference i.m. injection were equivalent in terms of $AUC_{0-\infty}$, with the 90% confidence interval of the geometric mean ratio for this parameter within the acceptance limits of 80.00–125.00%.

Although the C_{max} obtained for the test product administered as an i.v. bolus at the 5-s injection rate could not be directly compared in the study because no diclofenac solution for i.v. bolus injection is presently on the market, sufficient similarity was found between the values observed for this parameter in the 26 healthy volunteers participating in parts 2 and 3 of the study and the data published for Dyloject® 75 mg/2 mL to conclude that there was no actual difference in C_{max} between the two products. This could be expected, based on the fact that the two parenteral solutions contain the same amount of the same active substance and the same complexing agent (i.e. HPβCD) as the main excipient, and considering that the difference in volume between the two products (with volumes of 1 mL and 2 mL, respectively) is of no relevance, as small injected volumes are rapidly moved and dispersed in the overall blood flow following quick i.v. bolus administration in the cephalic or basilic veins (minimum blood flow of 40 mL/min, equivalent to 0.67 mL/s), two typical access sites for i.v. drug administration.

Hence, the pharmacokinetic profile described in our study supports the conclusion that no increased safety risks or additional safety concerns are expected for the diclofenac 75 mg/1 mL formulation administered by i.v. bolus when it is used to treat acute moderate–severe forms of pain, with a favourable benefit/risk profile based on proven comparability in terms of rate and extent of exposure with other approved diclofenac-containing parenteral formulations. Of note, published clinical data showed that the therapeutic efficacy of a single bolus i.v. dose of a diclofenac formulation containing HPβCD (Dyloject®) in treating postoperative dental pain due to fully or partially impacted mandibular third molar extraction, a well-known model for acute pain of moderate-to-severe intensity, was significantly superior to that of both placebo and 30-min i.v. infusion of Voltarol® over the initial 0–2 h as well as over the 0 to 4-h pain assessment interval, with more patients given Dyloject® than those given Voltarol® reporting a 30% reduction in pain intensity (52% vs. 21%) after 15 min [15]. A single i.v. dose of the diclofenac-HPβCD formulation was also found to deliver a similar response in terms of pain relief but with a significantly more rapid onset of action (5 min vs. 15 min) as compared to an i.v. bolus of 30 mg ketorolac, a NSAID with more preferential COX-1 selectivity than diclofenac and with a potentially less favourable safety profile, particularly at the gastrointestinal level [16]. These results suggest additional clinical benefit of diclofenac sodium solutions administered as an i.v. bolus over other diclofenac parenteral formulations administered by i.v. infusion.

5 Conclusion

Data generated in this study in support of the regulatory approval of the i.v. bolus route for Akis®/Dicloin®, a diclofenac sodium-containing small-volume (1-mL) solution for injection that is already licenced for i.m. and s.c. administration, showed that all available strengths (25 mg/mL, 50 mg/mL and 75 mg/mL) were safe and well tolerated at the systemic level and at the site of injection. The diclofenac rate and extent of exposure observed following i.v. bolus administration of the highest strength were clearly independent of the injection rate, which ranged between 5- and 30-s. Notably, the observed pharmacokinetic profile of the diclofenac sodium 75 mg/1 mL test product administered as a 5-s i.v. bolus indicates a more rapid onset and a higher concentration peak as compared to other marketed parenteral formulations and administration routes, suggesting a superior analgesic effect. This, together with the flexibility to select the most appropriate diclofenac dose based on the individual patient's needs and the higher confidence offered by a ready-to-use parenteral preparation, makes the new i.v. administration route for this product a very interesting therapeutic option for pain treatment, particularly in the peri- and postsurgical settings.

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Conflict of Interest VF and SR are employees of IBSA Institut Biochimique S.A.; CL and MRa are employees of CROSS Research SA. LL was an employee of CROSS Research S.A. until 31 August 2018. MRo was an employee of CROSS Research S.A. until 31 March 2019. CROSS Research S.A. was contracted by IBSA Institut Biochimique S.A. as a CRO to conduct this study and received financial support for its services. The authors declare that they have no other relationships or activities that influenced the submitted work.

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Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964

Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol (no. 14CH/DCiv11) was approved by the Ethics Committee of Canton Ticino, Switzerland and the Swiss Federal Health Authorities.

Informed Consent Informed consent was given by all subjects who participated in the study.

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