THE STUDY OF RELATIVE BIOAVAILABILITY OF OCULAR SUSPENSION OF 4-(5-METHYL-1,3,4-OXADIAZOLE-2-YL)-BENZENESULFONAMIDE IN RABBITS

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4-(5-methyl-1,3,4-oxadiazole-2-yl)-benzenesulfonamide (ODASA), which is a novel selective type II carbonic anhydrase inhibitor for treating open-angle glaucoma, is undergoing preclinical testing. Pharmacokinetics of the substance have only been studied in rats. Prior to clinical studies, it is necessary to assess the systemic exposure of ODASA in non-rodents. ODASA was administered to Soviet Chinchilla rabbits at a dose of 0.28 mg/kg. About 40 µl of ocular suspension of ODASA was instilled into each eye of animals from the first group, whereas the second group received intraperitoneal injections of the investigational drug. Each group consisted of 6 male rabbits. Samples were obtained prior to administration of ODASA and during 288 hours following the administration at 16 time points. A 10% ascorbic acid solution was added to plasma before freezing. The samples were analyzed using HPLC-MS/MS. Following eyedrop instillation, relative bioavailability for ODASA was 31% as compared to IP administration. Thus, as ODASA was well absorbed into the systemic circulation of rabbits following topical eyedrop instillation, testing its pharmacokinetics in healthy volunteers will be obligatory if the preparation proceeds to phase 1 of clinical studies.

Keywords: selective carbonic anhydrase inhibitor, pharmacokinetics, bioavailability, rabbit, plasma, open-angle glaucoma

Financing: the study was supported by the Ministry of Health of the Russian Federation (State assignment 1022051100011-8-3.1.5; 3.2.17 “Development of a drug for treatment of acute-angle glaucoma”).

Acknowledgement: the work was carried out in collaboration with the Scientific Department of the Institute of Pharmacy of Yaroslavl State Medical University, Yaroslavl.

Author contribution: Yaichkov II — experimental design development, analysis of rabbit plasma samples, performing statistical calculations, writing an article; Volkhin NN, Petukhov SS, Lazaryants OE — conducting the experiments on rabbits.

Compliance with ethical standards: the study was conducted in compliance with all ethical standards recommended in the Russian Federation. Rabbits were selected to evaluate the pharmacokinetic parameters and relative bioavailability of ODASA as other non-rodent species. The animals were kept in individual cages of a sufficient size. Access to water and mixed feed was available free-choice, except for 4 hours before administration and 2 hours after administration of the investigational preparation. The animals were housed at room temperatures of 20 °C, humidity of 40–65%, and a 12/12 h light–dark cycle. The experimental animals were under the supervision of a veterinarian throughout the experiment. Each group had a minimum allowable sample size for pharmacokinetic studies in the Russian Federation. This study was approved by the Independent Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Yaroslavl State Medical University of the Ministry of Health of the Russian Federation, Protocol No. 2 dated 04/20/2025.

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Received: 23.07.2025 **Accepted:** 23.10.2025 **Published online:** 09.11.2025

DOI: 10.24075/medet.2025.020

ИЗУЧЕНИЕ ОТНОСИТЕЛЬНОЙ БИОДОСТУПНОСТИ ГЛАЗНОЙ СУСПЕНЗИИ 4-(5-МЕТИЛ-1,3,4-ОКСАДИАЗОЛ-2-ИЛ)-БЕНЗОЛСУЛЬФОНАМИДА НА КРОЛИКАХ

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Новый селективный ингибитор карбоангидразы II типа 4-(5-метил-1,3,4-оксадиазол-2-ил)-бензолсульфонамид (ODASA) для лечения открытоугольной глаукомы проходит доклинические испытания. В настоящий момент его фармакокинетика изучена только на крысах. Перед началом клинических исследований ODASA необходимо оценить его системную экспозицию на втором виде животных, который не относится к грызунам. ODASA вводили кроликам породы «Советская Шиншила» в дозе 0,28 мг/кг. Первой группе проводили инстилляцию глазной суспензии в каждый глаз в объеме около 40 мкл, второй группе — ее внутрибрюшинное введение. В состав каждой группы входило по 6 особей мужского пола. Образцы крови отбирались до введения ODASA, а также на протяжении 288 ч после его введения в 16 временных точках. До заморозки к полученной плазме добавлялся 10% раствор аскорбиновой кислоты. Анализ образцов проводили методом ВЭЖХ-МС/МС. Величина относительной биодоступности действующего вещества после глазной инстилляции по сравнению с внутрибрюшинной инъекцией составила около 31%. Таким образом, из-за всасывания ODASA в системный кровоток при местном применении у крыс и у кроликов в случае проведения первой фазы клинических испытаний обязательно изучение его фармакокинетики на здоровых добровольцах.

Ключевые слова: селективный ингибитор карбоангидразы, фармакокинетика, биодоступность, кролик, плазма, открытоугольная глаукома

Финансирование: исследование поддержано Министерством здравоохранения Российской Федерации (государственное задание 1022051100011-8-3.1.5;3.2.17) «Разработка лекарственного препарата для лечения остроугольной глаукомы»).

Благодарности: работа выполнена в содружестве с научным отделом Института фармации Ярославского государственного медицинского университета, Ярославль.

Вклад авторов: И. И. Яичков — разработка дизайна эксперимента, анализ образцов плазмы кроликов, выполнение статистических расчетов, написание статьи; Н. Н. Вольхин, С. С. Петухов, О. Э. Лазарянц — проведение экспериментальной части на кроликах.

Соблюдение этических стандартов: исследование выполнено с соблюдением всех этических стандартов, рекомендованных в Российской Федерации. Кролики были выбраны для оценки фармакокинетических параметров и относительной биодоступности ODASA в качестве второго вида, который не относится к грызунам. Животные содержались в индивидуальных клетках достаточной площади. Доступ к воде и комбикорму ограничивался за 4 часа до и 2 часа после введения изучаемого препарата. На протяжении оставшейся части эксперимента питье и питание были свободными. В виварии был 12-часовой цикл смены освещения, температура — 20–25 °C и влажность — 40–65%. Подопытные животные на протяжении всего эксперимента находились под наблюдением ветеринара. Объем выборки в каждой исследуемой группе был минимально

допустимым согласно требованиям к проведению фармакокинетических исследований, рекомендованных в Российской Федерации. Данное исследование получило одобрение независимого этического комитета Федерального государственного бюджетного образовательного учреждения высшего образования «Ярославский государственный медицинский университет» Министерства здравоохранения Российской Федерации, протокол от 20.04.2025 № 2.

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Статья поступила: 23.07.2025. **Статья принята к печати:** 23.10.2025 **Опубликована онлайн:** 09.11.2025

DOI: 10.24075/medet.2025.020

Novel selective type II carbonic anhydrase inhibitor 4-(5-methyl-1,3,4-oxadiazole-2-yl)-benzenesulfonamide (ODASA) (Fig. 1A) is a promising new molecule for treating open-angle glaucoma. The compound is undergoing preclinical testing. It has been shown to lower intraocular pressure after topical ocular dosing. ODASA reduces the risk of any systemic adverse drug reactions. Its effect can last up to 24 hours [1]. 1% ophthalmic suspension of ODASA has been currently engineered. In rats, relative bioavailability (RB) is over 80% when the preparation is instilled in the eye compared to an intraperitoneal administration. ODASA enters the systemic circulation and is then hydroxylated. The main reaction involves the methyl group on the 1,3,4-oxadiazole ring, leading to the formation of 4-[5-(hydroxymethyl)-1, 4-oxadiazole-2-yl]-benzenesulfonamide (M1) (Fig. 1B). The minor reaction affects the sulfonamide group, forming the metabolite N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (M2) (Fig. 1C) [2].

According to regulatory requirements, the study of pharmacokinetics and bioavailability should be conducted in two species (one non-rodent) [3]. In this case, rabbits are commonly used. They are the most affordable lab animal species [4–7]. Beagle dogs [8–9], minipigs [10–11], and monkeys [12–14] are less frequently used as a second species. ODASA shows limited solubility in water, which makes its intravenous administration difficult and study of absolute bioavailability impossible. Thus, RB is calculated following intraperitoneal injection.

High-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) is the most common method for analyzing biological samples in pharmacokinetic studies. An express method has been developed for quantitative determination of ODASA and its hydroxylated derivatives in laboratory animal blood plasma. Protein precipitation was used to prepare samples. The minor metabolite N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide is chemically unstable in biological objects. Therefore, stabilization with a 10% ascorbic acid solution is necessary after plasma sampling [2].

Thus, the work is aimed at calculation of pharmacokinetic parameters and relative bioavailability of ocular suspension of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide in rabbits by analyzing samples with HPLC-MS/MS.

MATERIALS AND METHODS

The study was conducted using 3–4-month-old Soviet Chinchilla male rabbits obtained from the SMK Stezar nursery. It was a parallel group study investigating RB. The design was used because of deposition of ODASA within erythrocytes and its long half-life [2]. According to the ethical principles, the sample

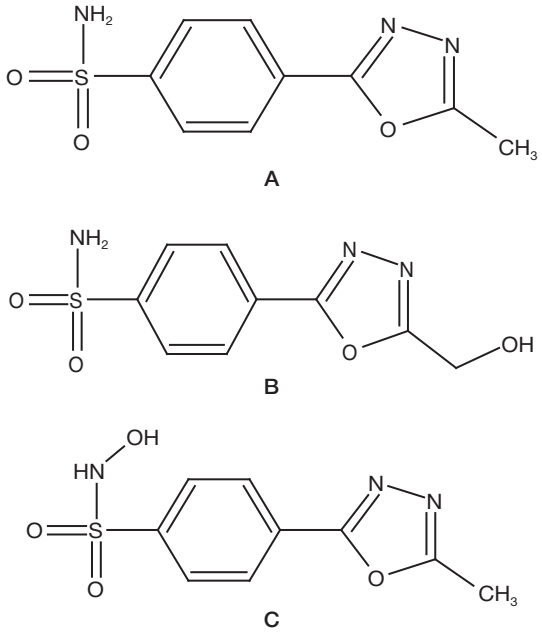


Fig. 1. Structures of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide and its metabolites 4-[5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl]-benzenesulfonamide (B) and N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (C)

size was minimally allowable for pharmacokinetic studies [3, 15]. A vivarium housed animals in comfortable conditions using individual cages. Access to water and mixed feed was available free-choice, except for 4 hours before administration and 2 hours after administration of the investigational preparation. Blood sampling from the lab animals was quick and relatively painless. Thus, no anesthesia was used. This study was approved by the Independent Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Yaroslavl State Medical University of the Ministry of Health of the Russian Federation, Protocol No. 2 dated 04/20/2025.

About 40 µl of 1% ocular suspension of ODASA was instilled into each eye (EI) of animals from the first group, including 6 rabbits weighing 2.84 ± 0.05 kg (M± SEM). It corresponded to a dose of 0.28 mg/kg. 6 other animals with a weight of 3.13 ± 0.05 kg (M±SEM) received an equivalent dose of intraperitoneal (IP) injections of the investigational drug. A 0.2 mL blood sample was drawn from a vein using an insulin syringe as in other similar studies [4–6]. Samples were obtained prior to administration of ODASA and at 30 min, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 192 hours, 240 hours, and 288 hours following the administration. K_3EDTA was chosen as an anticoagulant. The plasma obtained after centrifugation was stabilized with a 10% ascorbic acid solution in a 1:2 volume ratio (ascorbic acid solution: plasma). The samples were stored at or below — 70 °C till analysis.

A validated bioanalytical technique was used to quantitatively measure the concentration of ODASA and its metabolites. The solution of methanol containing 4-(3-methyl-6-oxo-5,6-dihydropyridazine-1(4H)-yl)-benzenesulfonamide, an internal standard, was added to precipitate the proteins and prepare the samples. To do that, a 100 µl reagent was combined with 20 µl of stabilized plasma. The mixture was stirred and centrifuged for 5 min at 10,000 rpm. The supernatant was transferred to micro-inserts and analyzed. A HPLC-MS/MS system was used, including Agilent 1260 Infinity chromatograph (Germany) and AB Sciex QTRAP5500 mass spectrometer (Singapore). Kinetex Phenyl-Hexyl column (50*4.6 mm, 2.6 microns) and Phenyl SecurityGuard Ultra Catridge pre-column (4.6 mm, 2.6 microns) were used for chromatographic separation. The Multiple Reaction Monitoring (MRM) mode was employed to detect the analytes and the internal standard [2]. The analytical range of plasma concentrations measured was 2–2000 ng/ml for ODASA and M1, and 0.5–500.0 ng/ml for M2.

Non-compartmental analysis was used to determine the pharmacokinetic parameters. Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), the area under the pharmacokinetic curve capturing drug exposure from time zero to the last measurable concentration (AUC_{0-t}), the area under the curve from zero to infinity ($AUC_{0-\infty}$), half-life ($T_{1/2}$), mean residence time (MRT), apparent volume of distribution (Vd/F), and apparent clearance (Cl/F) were calculated for ODASA and its metabolites using R v. 3.3.2 (Bear v. 2.7.7) package software.

The rate of conversion (R(M)) of the active substance into a metabolite was calculated using the formula:

$$R(M)=\frac{AUC_{0-\infty}\ (M)}{AUC_{0-\infty}\ (ЛС)}\times 100\%,$$

where $AUC_{0-\infty}$ (M) is $AUC_{0-\infty}$ of plasma metabolite;
$AUC_{0-\infty}$ (Drug) is $AUC_{0-\infty}$ of ODASA.

THE RESULTS OF THE STUDY AND THEIR DISCUSSION

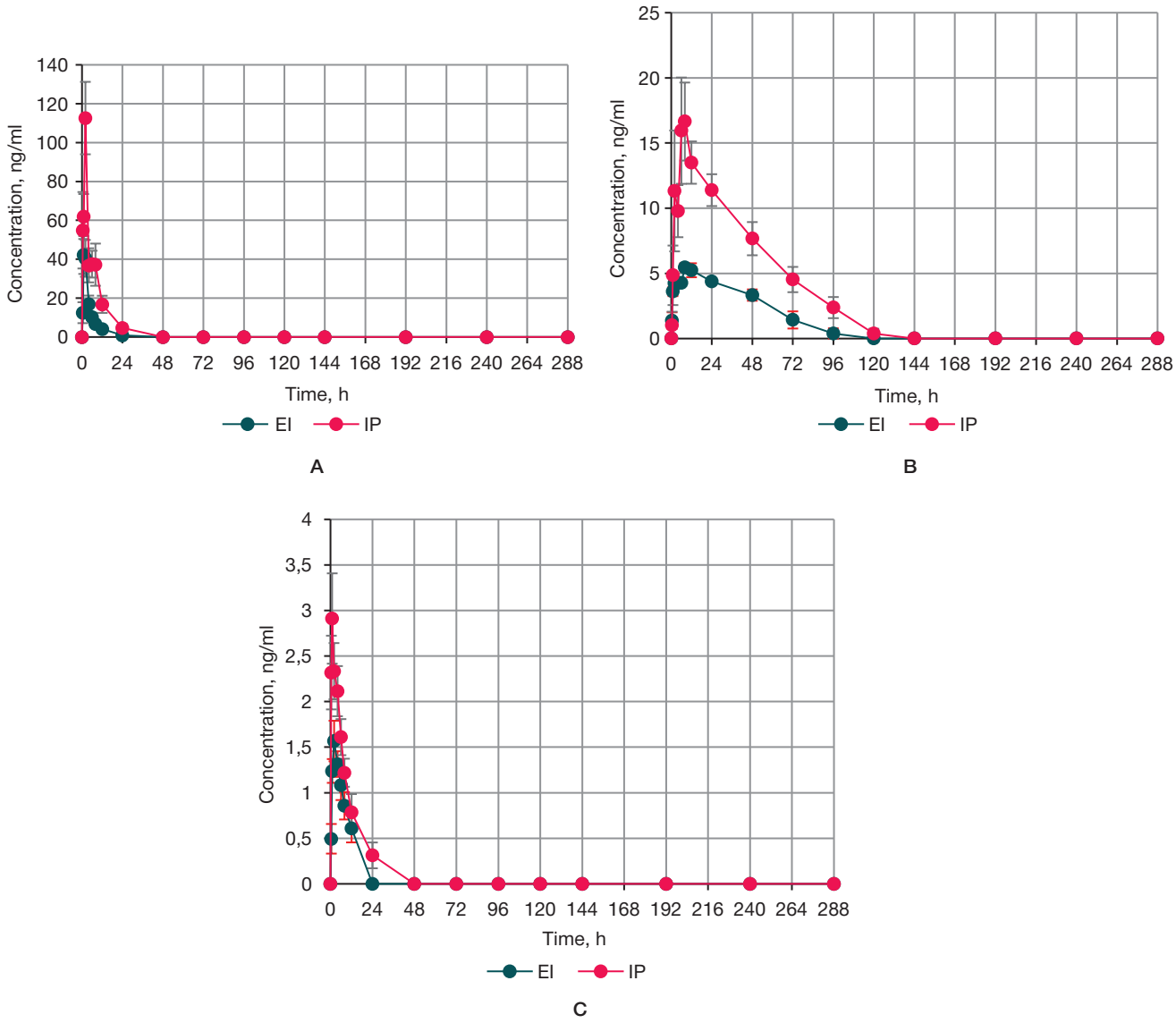
ODASA peak plasma concentration was 58.6 ± 7.2 ng / ml (M ± SEM) within 1 h after therapeutic administration (table). After 48 hours, the content of the active substance in this biological fluid was below the lower limit of quantitation (LLOQ) (Fig. 2A). Following eyedrop instillation, RB for ODASA was 30.76% as compared to IP administration, which is 2.5-fold lower than that in rats. In both modes of administration, the half-life of ODASA was over 6 times shorter than that in rats [2].

Following eyedrop instillation, T_{max} of main metabolite M1 occurred later than that of ODASA and M2. It was detected in plasma over the time range from 0 to 120 hours (Fig. 2B). Its $T_{1/2}$ was about 1.5 times shorter than in rats [2]. The peak concentration of the N-hydroxy derivative was reached from

Table. Pharmacokinetic parameters of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide and its metabolites in rabbit plasma

Preparation		ODASA (*n* = 6)		M1 (*n* = 6)		M2 (*n* = 6)	
Mode of administration		EI	IP	EI	IP	EI	IP
C_{max}, ng/ml	M ± SEM	58.6 ± 7.2	129.8 ± 11.4	5.9 ± 0.4	21.59 ± 2.73	1.66 ± 0.20	3.37 ± 0.4
$T_{max,\ h}$	Median (min.-max)	1.0 (1.0–2.0)	2(0.5–2.0)	8 (8–12)	7.0 (2.0–12.0)	1.5 (1.0–2.0)	1.0 (0.5–2.0)
$AUC_{0-t,}$ ng*h/ml	M ± SEM	188 ± 19	611 ± 91	256 ± 41	744 ± 73	11.9 ± 1.6	24.4 ± 4.7
$AUC_{0-\infty,}$ ng*h/ml	M ± SEM	210 ± 22	670 ± 100	430 ± 47	904 ± 100	21.5 ± 3.2	32.6 ± 6.4
$T_{1/2,}$ h	M ± SEM	5.2 ± 1.1	5.7 ± 1.1	48.2 ± 4.2	33.6 ± 5.0	9.4 ± 1.7	9.2 ± 1.9
MRT, h	M ± SEM	4.8 ± 0.8	6.2 ± 0.9	28.9 ± 3.4	34.9 ± 4.7	5.2 ± 0.3	6.6 ± 1.0
Cl/F, ml/h	M ± SEM	498.4 ± 46.4	169.8 ± 28.3	245.7 ± 24.9	120.6 ± 18.5	5141 ± 682	3816 ± 788
Vd/F, ml/kg	M ± SEM	3664 ± 733	1418 ± 429	16730 ± 1686	5276 ± 510	64388 ± 7033	40855 ± 2969
R(M)	M ± SEM	–	–	2.122±0.292	1.513±0.301	0.106±0.017	0.050±0.008

Note: ODASA — 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide; M1 — 4-[5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl]-benzenesulfonamide; M2 — N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide; EI — eyedrop instillation; IP — intraperitoneal administration.



Note: EI— eyedrop instillation; IP — intraperitoneal administration.

Fig. 2. Pharmacokinetic profiles of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (A) and its metabolites 4-[5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl]-benzenesulfonamide (B) and N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (B) in rabbit plasma (error intervals: ± SEM)

1 hour to 2 hours after instillation, just like in the case of the active substance (Fig. 2C). Following eyedrop instillation, $T_{1/2}$ of M2 was about 10 hours. It is approximately 3 times shorter than in rats [2]. The compound concentrations in plasma samples were lower than the LLOQ at 24 hours following instillation in the eye and at 48 hours following intraperitoneal administration.

In experiments with rabbits, ODASA and its metabolites had high apparent volume of distribution (table). They were significantly higher than the actual volume of circulating blood. It means that the investigational agents penetrate well into the organs and tissues of animals.

While using the therapeutic method of administration, the rate of conversion of ODASA to M1 was 2.122 ± 0.292, whereas the rate of conversion of ODASA to M2 was 0.106 ± 0.017 (M ± SEM). This is approximately 10 times higher than the values of R(M) of these hydroxylation products of the active substance calculated in rats. The difference can be explained by a lower preparation dose per unit of body weight and lower plasma concentrations of ODASA. The active centers of microsomal enzymes were less saturated, and ODASA biotransformation occurred much faster. For this reason, clearance values of ODASA in rabbits after EI are over 40 times higher than in rats [2].

Thus, ODASA was well absorbed into the systemic circulation of rabbits following topical eyedrop instillation. High relative bioavailability of the active agent was also detected in the pharmacokinetic study in rats. If the preparation proceeds to phase 1 of clinical studies, testing its pharmacokinetics in healthy volunteers will be obligatory.

CONCLUSIONS

1. ODASA can enter the systemic circulation of rabbits if instilled into the eyes.
2. Relative bioavailability of ODASA after instillation into the eyes was 30.76% compared with intraperitoneal administration.
3. The rate at which ODASA and its metabolites are eliminated differs across species. It is faster in rabbits than in rats.
4. As ODASA is absorbed after topical application in animals, the list of phase I clinical trials should include the study of pharmacokinetics.

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