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MONOGRAPH

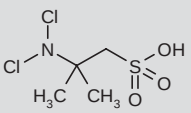
# NVC-422

*Antiinfective Agent*
*Treatment of Impetigo*
*Treatment of Conjunctivitis*
*Treatment of Urinary Tract Infections*

AL-46383A
DCDMT

2-(Dichloroamino)-2-methylpropane-1-sulfonic acid
*N*,*N*-Dichloro-2,2-dimethyltaurine

InChI: 1S/C4H9Cl2NO3S/c1-4(2,7(5)6)3-11(8,9)10/h3H2,1-2H3,(H,8,9,10)



$C_4H_9Cl_2NO_3S$
Mol wt: 222.09
CAS: 846056-87-9
EN: 432268


## SUMMARY

*NVC-422 is a first-in-class synthetic stable chlorotaurine exhibiting a broad spectrum of activity against Gram-positive and Gram-negative pathogens, without the potential for developing drug resistance. NovaBay has named these novel agents Aganocide® compounds. The company is developing various nonsystemic formulations of this active agent for use in multiple phase II clinical trials for various indications, including urinary catheter blockage and encrustation (UCBE), conjunctivitis and impetigo. Preclinical and clinical studies demonstrated that NVC-422 has a good safety profile and solution stability. NVC-422 is cidal to pathogens by the oxidative modification of sulfur-containing amino acids, such as methionine and cysteine, resulting in protein inactivation. Pathogens die within minutes after exposure to lethal concentrations of NVC-422, as measured by time-kill assays. Multiple passage studies against pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA), show no drug resistance. Its mechanism of action, fast time-kill and no observation of drug resistance uniquely differentiate NVC-422 from traditional antibiotics.*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*Synthesis prepared by S. ShankharaRaman, C. Estivill, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

## SYNTHESIS*

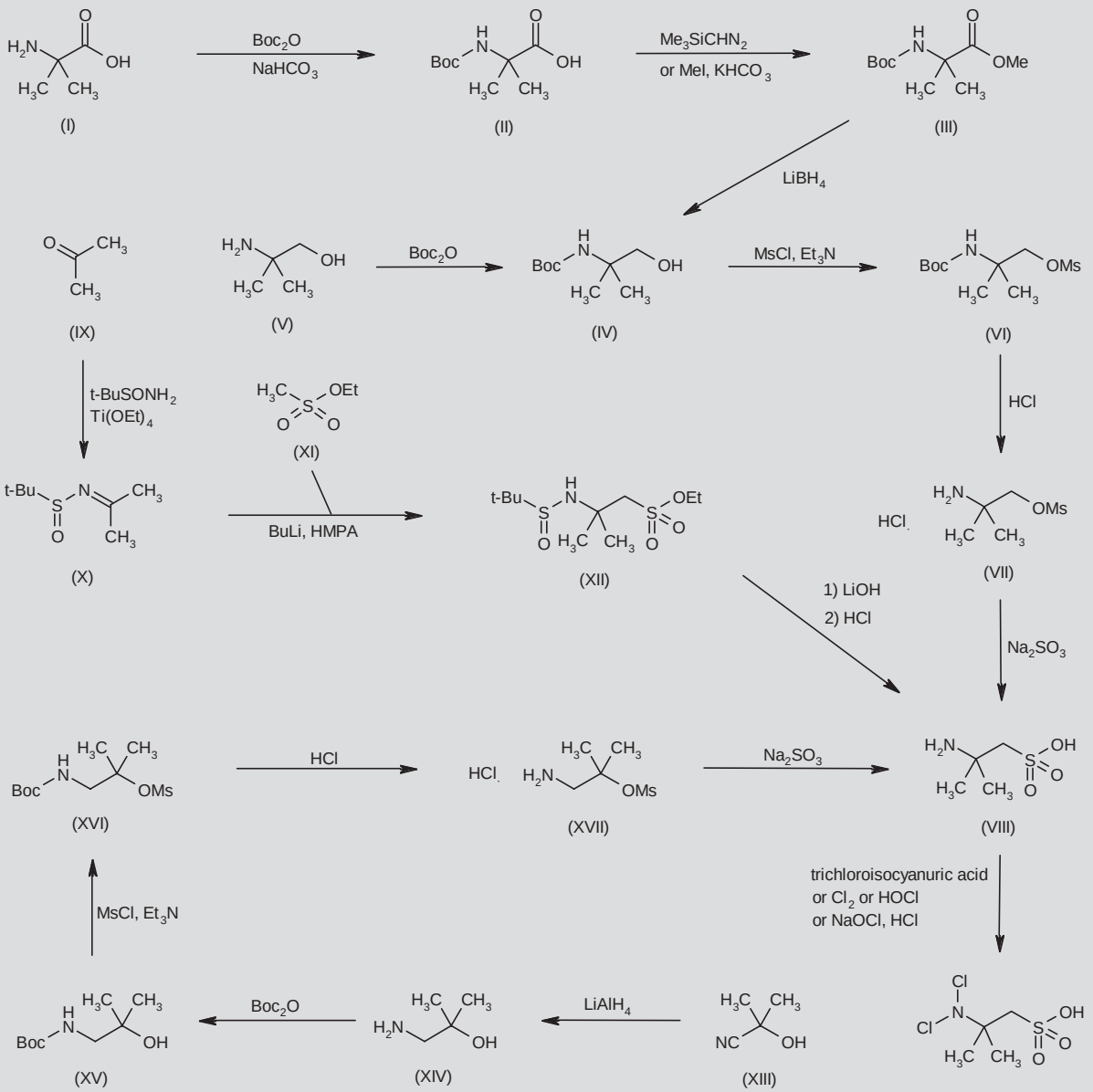
*N*-Protection of 2-methylalanine (I) with $Boc_2O$, optionally in the presence of $NaHCO_3$, in $THF/H_2O$ (1) yields *N*-Boc-2-methylalanine (II) (1, 2), which is then methylated with $Me_3SiCHN_2$ in MeOH/THF (1) or with MeI using $KHCO_3$ in DMF (2) to give the methyl ester (III) (1, 2). Reduction of the ester (III) by means of $LiBH_4$ in THF (2)/EtOH (1, 2) affords the primary alcohol (IV) (1, 2), which can also be prepared from 2-amino-2-methyl-1-propanol (V) by *N*-protection with $Boc_2O$ in $CH_2Cl_2$ (3). After conversion of alcohol (IV) to the corresponding mesylate (VI) with MsCl and $Et_3N$ in $CH_2Cl_2$, *N*-deprotection with HCl in dioxane provides amine (VII), which by reaction with $Na_2SO_3$ in $H_2O$ yields the aminosulfonic acid (VIII) (1-3). Finally, compound (VIII) is *N*-chlorinated using trichloroisocyanuric acid (1), $Cl_2$ (2-5), HOCl (5) or NaOCl/HCl (6). Scheme 1.

The aminosulfonic acid (VIII) can also be prepared by the following two strategies:

Condensation of acetone (IX) with *t*-$BuSONH_2$ by means of $Ti(OEt)_4$ gives the *N*-sulfinylimine (X), which is then coupled with ethyl methanesulfonate (XI) in the presence of BuLi and HMPA in THF to produce the propanesulfonate derivative (XII). Finally, hydrolysis of the sulfonate ester (XII) with LiOH in $THF/MeOH/H_2O$, followed by removal of the sulfinyl protecting group with HCl in MeOH furnishes aminosulfonic acid (VIII) (1). Scheme 1.

Reduction of 2-hydroxy-2-methylpropanenitrile (XIII) by means of $LiAlH_4$ yields 1-amino-2-methylpropan-2-ol (XIV), which is then *N*-protected with $Boc_2O$ to give *N*-Boc-1-amino-2-methylpropan-2-ol (XV). Mesylation of the alcohol (XV) with MsCl using $Et_3N$ in $CH_2Cl_2$ and subsequent *N*-deprotection of the resulting mesylate (XVI) with HCl in dioxane affords the amino mesylate (XVII). Finally, substitution of the tertiary mesylate (XVII) with $Na_2SO_3$ occurs with rearrangement of the primary amino group generating aminosulfonic acid (VIII) (2, 6). Scheme 1.

**Scheme 1.** Synthesis of NVC-422




## BACKGROUND

Microbial resistance is emerging faster than we are replacing our armamentarium of antimicrobial agents. The current public health war against bacterial infections is rapidly approaching a critical stage, in which bacterial resistance to antibiotics becomes widespread and our reservoirs of available antibiotics and viable therapeutics are depleted. During the past 60 years, the rise in the frequency of resistance, particularly to multiple drugs, has thwarted the treatment of patients in the hospital and the community (7, 8).

As a consequence, there is an evolving unmet medical need for novel antimicrobial agents that are effective against resistant pathogens and that carry a low potential for the development of drug resistance. Efforts focusing on the screening of large combinatorial chemical libraries for promising antimicrobial compounds have been rather disappointing (9). Likewise, attempts to identify novel cationic peptides (10), target-driven screening (11) and focused library screening have also not paid sufficient dividends. Nonspecific biocides are another important class of antibacterial compounds wide-

ly used in topical applications, but despite their nonspecific mechanisms of action, the occurrence of bacteria which are resistant to both biocides and antibiotics is increasing (12, 13).

As part of the innate immune system, leukocytes are capable of generating and releasing reactive oxygen species (14). During oxidative burst, neutrophils selectively generate hypochlorous acid to destroy invading microbial pathogens. In a secondary reaction, hypochlorous acid reacts with taurine, a semi-essential amino acid, resulting in *N*-chlorotaurine (NCT) and *N*,*N*-dichlorotaurine (NNDCT), which have antimicrobial and antiinflammatory effects (15-17). NCT has shown significant bactericidal and fungicidal properties with relatively low toxicity compared to other oxidants. However, NCT does not possess the long-term solution stability needed for the production and marketing of a nonsystemic therapeutic (4).

NovaBay Pharmaceuticals, Inc. has designed a research program to enhance the activity and stability of the Aganocide® family of compounds (1, 4, 18, 19). NVC-422, a synthetic analogue of NCT, is the first in a class of Aganocide® compounds that has been clinically tested for the nonsystemic management of microbial infections. NVC-422 has the same broad-spectrum, fast-acting profile as NCT plus the advantage of long-term solution stability at therapeutically safe concentrations, as outlined below, that are well tolerated (20) and provide effective antimicrobial activity (21).

NVC-422 is currently in phase II clinical trials for a number of antimicrobial applications, including the treatment of impetigo as a topical gel (20), for solution instillation into a Foley catheter for the prevention of urinary catheter blockage and encrustation (UCBE), and as eye drops for the treatment of adenoviral conjunctivitis. These indications are nonsystemic, where topical application of a solution or gel exerts its antimicrobial effects locally, and NVC-422 is not readily absorbed through the skin, bladder or eyes (unpublished results).

## PRECLINICAL PHARMACOLOGY

NVC-422 is a broad-spectrum, fast-acting antimicrobial agent that is effective against Gram-positive and Gram-negative bacteria, fungi and viruses. This makes NVC-422 effective against the ESKAPE pathogens (*Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa* and *Enterobacter* species) that cause multidrug-resistant clinical infections, dermatophytes and a wide range of viruses, including, but not limited to, adenoviruses (21-24). Furthermore, no bacterial isolates with decreased susceptibility were detected for *P. aeruginosa*, *E. coli* or *S. aureus* in multiple passage experiments (manuscript in preparation), whereas commercially available antimicrobial compounds, such as ciprofloxacin, retapamulin, mupirocin and fusidic acid, all suffer from the development of resistance under serial passage conditions (22, 25, 26).

Our mechanism of action studies indicate that NVC-422 is cidal to pathogens by the oxidative modification of sulfur-containing groups, such as methionine and cysteine, resulting in protein inactivation. Time-kill assays show bactericidal activity (> 99.99% kill) in less than 5 minutes at pH 4 and in less than 15 minutes at pH 7 at minimum bacterial concentrations (21). These features of the mechanism of action, fast time-kill and no observation of drug resistance differentiate NVC-422 from more traditional antibiotics.

## SAFETY

A comprehensive battery of GLP safety pharmacology and toxicology studies has been conducted to support the use of NVC-422 in a number of clinical indications under several Investigational New Drug (IND) applications. A complete panel of safety pharmacology studies (central nervous system, respiratory and cardiovascular) has yielded no remarkable findings. The following nonsystemic toxicology studies designed to establish initial safety for each clinical route of administration and regimen have been completed: nasal, ocular, bladder and dermal.

The determined "no adverse effect levels" were used to establish the maximum initial dose for clinical trials designed to evaluate nasal decolonization, conjunctivitis, impetigo, acne and bladder irrigation. Subsequent human safety studies have confirmed that doses and regimens expected to provide clinical benefit have been well tolerated, with no severe adverse events reported.

## CLINICAL STUDIES

Clinical studies using NVC-422 are outlined in Table I.

***Table I.*** *Examples of clinical studies evaluating NVC-422.*

| Indication | Purpose | Clinical trial |
|---|---|---|
| Impetigo | This is a randomized, double-blind study comparing 0.1%, 0.5% and 1.5% NVC-422 topical gel in children with impetigo | NCT01367314 |
| CAUTI | The purpose of this clinical trial was to study the effects of NVC-422 instilled into the bladder in reducing bacteria in the urine | NCT00781339 |
| UCBE | The use of a catheter irrigation solution that can prevent biofilm formation and encrustation leading to blockage may keep the catheter patent longer, resulting in fewer catheter changes, a potentially lower incidence of UTIs and better patient quality of life | NCT01243125 |
| Adenoviral conjunctivitis | The purpose of this study is to evaluate the safety and efficacy of NVC-422 ophthalmic solution for the treatment of adenoviral conjunctivitis | NCT00901693 |

CAUTI, catheter-associated urinary tract infection; UCBE, urinary catheter blockage and encrustation; UTIs, urinary tract infections.

### Impetigo

A randomized, sequential-group, double-blind phase IIa study evaluated the efficacy and safety of 3 different strengths of NVC-422 gel formulation administered 3 times a day for 7 days to male and female subjects 2-12 years of age (ClinicalTrials.gov Identifier: NCT01367314). The objectives of this study were to compare the efficacy and safety of three different strengths of NVC-422 (0.1%, 0.5% or 1.5%) in the treatment of primary non-bullous impetigo. Subjects were randomly assigned to receive either a low dose (0.1% NVC-422 gel) or higher doses (0.5% or 1.5% NVC-422 gel) during two study periods in a 1:2 ratio. A total of 129 subjects were enrolled and randomized (20).

Clinical evaluation of the target lesion and global evaluation of all treated lesions occurred at end of treatment (EOT) (day 8) and at follow-up on day 15. A Skin Infection Rating Scale (SIRS) was recorded by the investigator (who was unaware of the treatment assignment) for the target lesion to determine the clinical response. Five primary signs and symptoms were included in the SIRS score, which comprised exudate/pus, crusting, erythema/inflammation, itching and pain, and were graded by the investigators on a scale ranging from absent (0) to severe (3). Safety endpoints included study treatment discontinuations, adverse events (AEs) on treatment and serious adverse events (SAEs).

Clinical efficacy assessment was determined by the proportion of subjects in each treatment group who were considered a clinical responder (clinical success + clinical improvement) at EOT and at follow-up test of cure 1 week later. The criteria for outcome of a clinical responder included an SIRS score of 0 for exudate/pus and did not require any additional antimicrobial therapy to treat the impetigo. Patient bacteriological efficacy assessment was determined by the proportion of subjects in each treatment group who were considered a bacteriological success; that is, the causative pathogen isolated from the target lesion at baseline, *S. aureus* and/or *S. pyogenes*, is eliminated on culture, or clinical response is such that no exudate material was present for culture, and therefore is presumptive evidence of pathogen eradication at EOT and at follow-up test of cure. Subjects were excluded if systemic or topical antibiotics or steroids were given within 3 days of study entry or if they had any current infection (including impetigo) that would require systemic antibiotic therapy.

The clinical response at EOT (day 8) showed a response rate of 85%, 87% and 92%, respectively, for the 0.1%, 0.5% and 1.5% gel in the per-protocol complete (PPC) subset population. The bacteriological response (as defined above) showed a similar response rate of 87%, 90% and 95%, respectively. Similar clinical and bacteriological responses were seen in the modified intent-to-treat population.

All subjects who were clinical responders (success or improvement) at day 8 and returned for their follow-up visit at day 15 became a clinical success (SIRS score = 0). There was no recurrence of infection at day 15 in any of the three treatment groups. Infections were predominantly caused by *S. aureus*, either as a single organism or a mixed infection with *S. pyogenes*.

All three doses of NVC-422 evaluated were well tolerated by the subjects. No SAEs occurred in the study. All AEs reported (nine in total) were mild to moderate in severity and all resolved.

### Urinary catheter

There have been two studies conducted and completed with NVC-422 solution as a bladder irrigant. The initial placebo-controlled safety study in normal healthy volunteers was a single-dose, sequential-cohort, concentration-escalation design. Subjects were dosed with two 50-mL instillations of NVC-422 into the bladder via urinary catheter and retained for 15 minutes before draining, starting at 0.01%; the next cohort was dosed at 0.02%, the third cohort at 0.05% and the last cohort at 0.1%. Based on the absence of any dose-limiting toxicity, the maximum tolerated dose (MTD) was set, and an expanded cohort was treated at this MTD in the same manner as the single dose once daily for 7 consecutive days in part 2 of the study.

Blood samples were collected during the multiple-dose phase of the study, predose, and at 5, 10, 30, 60, 120, 240 and 360 minutes (after instillation had been completed) on days 1 and 7 for quantitation of NVC-422 and 2,2-dimethyltaurine (2,2-DMT; i.e., the NVC-422 parent amine).

A total of 29 subjects were enrolled, all of whom completed the study, and there were no dropouts. In the single-dose phase of the study, 5 of 12 (42%) subjects who received NVC-422 experienced an AE compared to 3 of 8 (38%) subjects who received placebo. The most common AE in both treatment groups (active and placebo) was urinary urgency after catheter removal and was judged to be related to the catheterization procedure itself.

In the multiple-dose phase, the most common adverse event experienced in both treatment groups (active and placebo) was hematuria, which was noted in all catheterized subjects. All hematuria resolved within 24 hours after removal of the catheter. Neither NVC-422 nor 2,2-DMT was detectable in any of the pharmacokinetic samples in any of the subjects. The study drug was well tolerated and there were no serious AEs in the single- or multiple-dose phase of the study.

The second clinical trial was an open-label, dose-escalating, pilot phase IIa study in chronically catheterized subjects with asymptomatic bacteriuria conducted with two different concentrations (0.1% and 0.2%). Objectives for this study included evaluating the antimicrobial effect of NVC-422 on bacteriuria and the safety in this patient population. Eligible subjects who had provided informed consent were enrolled in the study. Criteria for eligibility included having an indwelling transurethral catheter that was not scheduled to be exchanged for at least 1 week prior to enrollment and documented asymptomatic bacteriuria. Catheterized subjects with asymptomatic bacteriuria (> 100,000 cfu/mL) had urine samples collected through the sampling port of the bladder catheter at various time points on day 1. Subjects received an instillation of 25-100 mL of a solution of NVC-422 through the lumen of the indwelling bladder catheter, followed by draining of the bladder contents. Subjects then immediately received another instillation, which remained in the bladder for 60 minutes and was then drained. Instillation volumes were determined and dependent on the functional bladder capacity. Adverse events were recorded. Additional urine samples were also collected once daily on days 2, 4 and 7.

Similar procedures were carried out daily for 7 days in part 2 of this study. Subjects enrolled in part 2 also had blood samples collected

for plasma pharmacokinetics on day 1 and day 7 predose and at 1, 3 and 6 hours following drug instillation.

In the multiple-dose part of the study, some subjects had uropathogens that were eradicated by the end of the 7 days of treatment despite the presence of high urinary concentrations of > 100,000 cfu/mL of multiple organisms at baseline. In those patients completing all treatments, two of five who were treated with 0.1% NVC-422 and four of five subjects in the 0.2% NVC-422 arm had at least one pathogen that disappeared after treatment.

No patients experienced a serious AE in this study and the NVC-422 irrigation solution was well tolerated in all treatment groups. Less than half of the patients (45%; 9 of 20) experienced 1 or more AE. The distribution across the groups was approximately equivalent, with incidences for parts 1, 2a and 2b of 40% (2 of 5), 40% (2 of 5) and 50% (5 of 10), respectively. The majority of the AEs reported were mild to moderate in severity and most were considered by the investigator to be unrelated to study treatment. Two subjects experienced a mild transient burning sensation during treatment that resolved once the solution was drained.

NVC-422 was not detectable in plasma samples obtained at various times on days 1 and 7 in any of the patients; in two subjects very low levels of 2,2-dimethyltaurine (NVC-422 parent amine) were detected.

### Adenoviral conjunctivitis

A randomized, double-masked, multicenter, parallel-group phase II study of NVC-422 ophthalmic solution compared to vehicle as control for the treatment of adenoviral conjunctivitis was conducted in the U.S. The randomization was done using NVC-422 ophthalmic solution (0.33%) versus vehicle 1:1. The patient eligibility was by diagnosis of adenoviral conjunctivitis in either eye by an adenovirus antibody test or a positive clinical diagnosis. The treatment dosing was 8 times per day for a treatment period of 10 days. The patients had clinical visits scheduled for days 1, 3, 5, 7, 9, 11 and 18. The patients were evaluated for clinical signs and symptoms of conjunctivitis and PCR was used for determining the presence of adenovirus and serotypes. A safety evaluation was done on all subjects enrolled. An efficacy evaluation was done only on patients with confirmed adenoviral infection by laboratory findings. A total of 81 subjects with confirmed adenoviral conjunctivitis were evaluated for efficacy. The data were strongly suggestive of a treatment effect in both clinical and microbiological findings in the subset of patients with serotypes associated with epidemic keratoconjunctivitis. Evidence of a decreased incidence of subepithelial infiltrates (SEIs) and less transmission of infection to the other eye was noted. A statistically significant improvement in sustained blurred vision clearing rate was found. The treatment was well tolerated, with no safety issues.

## CONCLUSION

Microbial resistance is emerging faster than we are replacing our armamentarium of antimicrobial agents. For impetigo, the overall clinical response rate (success and improvement) in the PPC population was excellent in each of the dose groups (85%, 87% and 92%, respectively, in the 0.1%, 0.5% and 1.5% dose groups). Bacteriological response rates were very similar to clinical response rates. AEs were mild to moderate in severity and predominantly consisted of local application site reactions. All AEs resolved after the end of treatment (20). For CAUTI, based on findings to date, the preliminary conclusion is that 0.2% NVC-422 instilled into the urinary bladder and retained for up to 1 hour is safe and well tolerated for 7 days of treatment. A multicenter study currently under way is exploring the impact of NVC-422 instillation on UCBE in chronically catheterized patients. For adenoviral conjunctivitis there was evidence of a decreased incidence of SEIs and less transmission of infection to the other eye was noted. A statistically significant improvement in sustained blurred vision clearing rate was found. The treatment was well tolerated, with no safety issues. The broad-spectrum activity, low probability of the development of drug resistance and good clinical tolerability may make NVC-422 an effective alternative to known antimicrobial compounds for the treatment of nonsystemic infections.

## SOURCE

NovaBay Pharmaceuticals, Inc. (US).

## DISCLOSURES

Rabih Darouiche, MD, is an investigator for NovaBay Pharmaceuticals. All other authors Ramin (Ron) Najafi, PhD, Kenneth Krantz, MD, PhD, Dmitri Debabov, PhD, Lisa Friedman, PhD, Behzad Khosrovi, PhD, Lu Wang, PhD, Susan Iovino, BSMT, and Mark Anderson PhD, are employees of NovaBay Pharmaceuticals, Inc.

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