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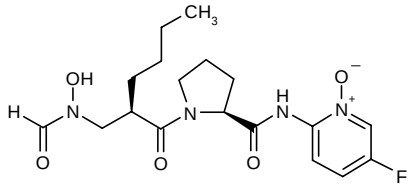
LBM-415

Antibacterial
Peptide Deformylase Inhibitor

NVP-PDF-713
VIC-104959

N-(5-Fluoro-1-oxidopyridin-2-yl)-1-[2(*R*)-(*N*-formyl-*N*-hydroxyaminomethyl)hexanoyl]-L-prolinamide
2(*R*)-Butyl-*N*-formyl-*N*-hydroxy-β-alanyl-*N*-(5-fluoro-1-oxido-2-pyridinyl)-L-prolinamide



$C_{18}H_{25}FN_4O_5$
Mol wt: 396.4165

CAS: 478913-91-6

CAS: 771478-85-4 (as calcium salt [2:1])

EN: 353520

Abstract

Resistance among bacterial pathogens has necessitated the search for novel targets in antimicrobial research. The peptide deformylase inhibitors are a novel and unique class of antimicrobial agents in development for the treatment of respiratory tract and skin infections. LBM-415 is the first such compound to enter clinical development. Its activity has been widely evaluated in preclinical studies against multiple pathogens, including drug-resistant strains. *In vitro* studies using recent clinical isolates have demonstrated potent activity against streptococcal and staphylococcal strains responsible for community-acquired respiratory tract infections and skin infections. LBM-415 is also active against medically important groups of drug-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci and clarithromycin-resistant *Helicobacter pylori*. The efficacy of LBM-415 has been demonstrated in mouse models of infection, where it was active against *Mycoplasma pneumoniae*-induced pneumonia, and had comparable efficacy to linezolid and vancomycin against systemic MRSA and methicillin-susceptible *S. aureus* (MSSA). Pharmacokinetic studies, including single- and multiple-dose studies in humans, demonstrated linear kinetics, with rapid absorption of LBM-415 and no evidence of accumulation. The compound is advancing to phase II/III clinical trials.

Synthesis

Reaction of 2-butylmalonic acid (I) with formaldehyde and piperidine gives 2-butylacrylic acid (II), which is first activated with pivaloyl chloride and DIEA and then condensed with the chiral oxazolidinone (III) by means butyl lithium in THF to yield the *N*-acyl-oxazolidinone (IV). Asymmetric addition of *O*-benzylhydroxylamine (V) to the double bond of compound (IV) by means of TsOH in ethyl acetate affords the chiral *N*-hexanoyl-oxazolidinone (VI), which is acylated at the hydroxylamine group with formic acid and acetic anhydride to provide formamide (VII). Cleavage of the chiral auxiliary oxazolidinone group of formamide (VII) by means of LiOH and H_2O_2 in THF/water gives 2(*R*)-(*N*-benzyloxy-*N*-formylaminomethyl)hexanoic acid (VIII), which is condensed with L-proline (5-fluoropyridin-2-yl)amide (IX) – prepared by condensation of 2(*S*)-(chlorocarbonyl)pyrrolidine-1-carboxylic acid benzyl ester (X) with 5-fluoropyridin-2-amine (XI) in pyridine to yield the prolinamide (XII) and then deprotection with AcOH/HBr – by means of DIEA and HATU in dioxane to yield the hexanamide (XIII). Oxidation of compound (XIII) with MCPBA provides *N*-(5-fluoro-1-oxidopyridin-2-yl)-1-[2(*R*)-(*N*-benzyloxy-*N*-formylaminomethyl)hexanoyl]-L-prolinamide (XIV), which is finally deprotected by means of H_2 over Pd/C in ethanol/ethyl acetate (1). Scheme 1.

Introduction

The development of resistance and cross-resistance among bacterial pathogens presents a significant challenge in the management of infections. The threat to the community, and the possibility that such strains can cause serious systemic infections in immunocompromised individuals, has resulted in the search for novel targets and mechanisms of action in antimicrobial research (2). Peptide deformylase is a highly conserved metalloproteinase that is critical to the maturation of bacterial proteins during translation in prokaryotic cells. It is not

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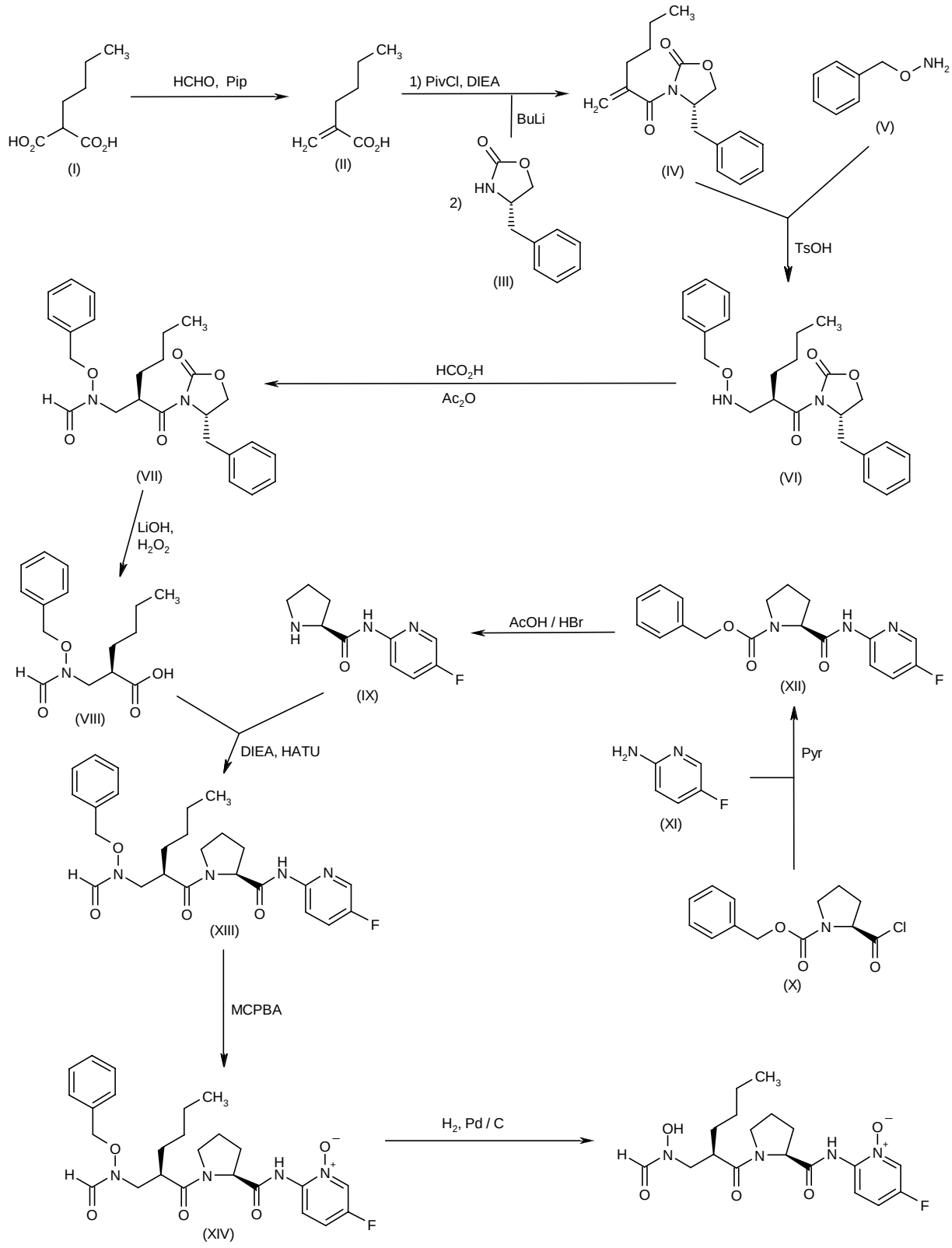
Scheme1: Synthesis of LBM-415



found in eukaryotic cells, making it a unique antibacterial target. This enzyme is the target for a new class of antimicrobial agents, the peptide deformylase inhibitors (3, 4). One such agent, LBM-415 (NVP-PDF-713, VIC-104959), is the first to enter clinical development for the treatment of respiratory tract and skin and soft tissue infections caused by susceptible Gram-positive and Gram-negative organisms (5).

Pharmacological Actions

LBM-415 has been evaluated against a range of bacterial pathogens, including resistant strains. The compound was tested against 1,837 Gram-positive clinical isolates cultured from North American and European patients during 2002. Minimum inhibitory concentrations inhibiting 50% and 90% of the tested strains (MIC_{50} and MIC_{90}, respectively) were used to determine the activity and spectrum against the organisms. The species rank order was *Staphylococcus aureus* > coagulase-negative staphylococci (CoNS) > streptococci > enterococci > *Listeria* spp. The LBM-415 MIC results against *S. aureus* and the CoNS strains were in the range of < 0.06-4 μg/ml, although the majority of staphylococci had MIC values between 0.25 and 2 μg/ml. LBM-415 MIC_{90} results were as follows: 1 μg/ml for *S. aureus*, β-hemolytic and viridans group streptococci and *Streptococcus bovis*, and 2 μg/ml for CoNS, *Streptococcus pneumoniae* and *Listeria* spp. The potency of LBM-415 was generally 2-fold lower against enterococci compared to its antistaphylococcal potency (MIC_{90} = 4 μg/ml). Resistance to other classes of agents did not influence the LBM-415 MIC values among enterococci (5, 6).

The antimicrobial activity of LBM-415 was further characterized against a worldwide collection of 1,306 clinical isolates from 2001 to 2002, selected to overrepresent resistant populations. LBM-415 was uniformly active against all *S. pneumoniae* strains, with MIC_{90} values of 0.5-1 μg/ml. It displayed activity against both *Haemophilus influenzae* and *Moraxella catarrhalis*. LBM-415 had a predominantly bacteriostatic action. Spontaneous single-step mutational rates at 8 x MIC were very low (10^{-6} to < 10^{-8}) for enterococci, *Streptococcus pyogenes*, *S. pneumoniae*, *M. catarrhalis*, *H. influenzae* and some strains of *S. aureus*. These rates assess the ability of bacterial species to develop resistance to a peptide deformylase inhibitor. Neither class-specific synergistic nor antagonistic interactions were observed with other antimicrobials. Kill curve experiments demonstrated bactericidal activity at 24 h at 4 or 8 x MIC against oxacillin-resistant *S. aureus*, oxacillin-susceptible CoNS, penicillin-resistant *S. pneumoniae* and *H. influenzae* (7).

The antimicrobial activity of LBM-415 was also determined against key upper respiratory isolates. It was active against a wide spectrum of bacteria, including *S. pneumoniae*, *M. catarrhalis* and *S. pyogenes* (MIC_{90} = 0.25-4 μg/ml). The MIC_{90} value against *H. influenzae* was 8 μg/ml. The postantibiotic effect, defined as the period of persistent inhibition of bacterial growth after drug removal from *in vitro* cultures, was evaluated against *S. pneumoniae* and *H. influenzae*, with values of 0.23 and 0.9 h, respectively. The sub-MIC effect, when strains were resuspended in broth in the presence of one-quarter the MIC, was significantly longer (3.6 and 2.4 h for *S. pneumoniae* and *H. influenzae*, respectively). The frequency of resistance to LBM-415 was low in both these bacterial species (8).

The *in vitro* activity of LBM-415 was also investigated against medically important groups of drug-resistant pathogens. LBM-415 exhibited potent activity against a range of important bacterial pathogens, in particular those associated with common respiratory tract infections. It was also active against *Helicobacter pylori*, *Mycoplasma pneumoniae* and *Mycoplasma genitalium* isolates. LBM-415 demonstrated equivalent activity against susceptible and multidrug-resistant isolates of methicillin-resistant *S. aureus* (MRSA), penicillin-resistant *S. pneumoniae*, vancomycin-resistant enterococci and clarithromycin-resistant *H. pylori*. The differences between the geometric mean MICs for susceptible *versus* resistant organisms were not statistically significant, indicating equivalent activity against both (9).

The antistaphylococcal activity of LBM-415 was evaluated against isolates of methicillin-resistant and -susceptible *S. aureus* and CoNS. The MICs ranged from < 0.06 to 4.0 μg/ml, and were similar for both methicillin-resistant and -susceptible strains. Time-kill assays showed that after 24 h, LBM-415 was bacteriostatic against all strains tested. LBM-415 was also active against the vancomycin-resistant *S. aureus* (VRSA) isolate HMC3, with an MIC of 0.5 μg/ml. It had a bacteriostatic effect after 24 h at 4 x MIC (10-14).

Thee antipneumococcal activity of LBM-415 was also examined against clinical isolates. The MICs ranged from 0.03 to 4.0 μg/ml, irrespective of the β-lactam, macrolide or quinolone resistance phenotype and genotype. LBM-415 was bactericidal against 6 strains after 24 h at 2 x MIC. The kill kinetics were similar to those of linezolid (15-17).

The activity of LBM-415 was further evaluated against 400 anaerobic clinical isolates of the *Bacteroides fragilis* group referred during 2002-2003 by U.S. medical centers. LBM-415 showed excellent *in vitro* activity against all the species (MIC = 0.03-0.5 mg/l; MIC_{90} = 0.5 mg/l). It was active against strains resistant to β-lactams, quinolones and clindamycin (18).

A total of 45 Gram-positive isolates resistant to oxazolidinones or streptogramin were isolated at surveillance sites in the U.S., Canada, Brazil and Europe. These organisms included *Enterococcus faecalis*, *Enterococcus faecium*, *S. aureus*, CoNS and *Staphylococcus oralis*. LBM-415 was active against all the isolates tested, with MICs of 4 mg/l or less (19).

The potency of LBM-415 was evaluated against a challenge set of strains of pathogenic *Neisseria* originating from global surveillance networks, which included representative resistant phenotypes. A total of 157 strains of

Neisseria gonorrhoeae, including strains with elevated MICs to fluoroquinolones, β-lactams and tetracyclines, and 100 strains of *Neisseria meningitidis*, including penicillin-resistant strains, were tested. LBM-415 was active against *N. meningitidis* with MICs in the range 0.5-4 μg/ml (MIC_{50} = 1 μg/ml). It was 2-4-fold less active against *N. gonorrhoeae* isolates, with MIC_{50} and MIC_{90} values of 4 and 8 μg/ml, respectively. Although LBM-415 demonstrated activity against both *Neisseria species*, it had limited utility against *N. gonorrhoeae*, and was less active against both species when compared with ceftriaxone, ciprofloxacin, penicillin and tetracycline (20).

The activity of LBM-415 was evaluated against 10 isolates each of *M. pneumoniae*, *Mycoplasma hominis* and *Ureaplasma* spp. It was highly active against all *M. pneumoniae* isolates, with MIC_{50} and MIC_{90} values of 0.0005 and 0.001 μg/ml, respectively, but it was much less active against *M. hominis* and *Ureaplasma* (21).

In Japan, antimicrobial resistance levels are very high among clinically significant Gram-positive organisms and community-acquired respiratory pathogens. Thus, the potency of LBM-415 was evaluated against 695 key Gram-positive pathogens, including *S. aureus*, *H. influenzae*, *S. pneumoniae* and CoNS, collected during surveillance in 2002 and 2003 in Japan. All *S. pneumoniae* were inhibited at 2 mg/l or less of LBM-415, irrespective of penicillin or multidrug resistance. The activity against *H. influenzae* was limited, particularly against β-lactamase-negative ampicillin-resistant strains, with MIC_{50} and MIC_{90} values of 4 and 32 mg/l, respectively. *S. aureus* and CoNS strains were all responsive to LBM-415, with MICs of 4 mg/l or less, irrespective of oxacillin susceptibility (22).

The efficacy of LBM-415 has been evaluated in mouse models of infection. Mice inoculated once with *M. pneumoniae* to elicit acute pneumonia were treated with LBM-415 (50 mg/kg) or placebo daily for 13 days. The MIC of LBM-415 against *M. pneumoniae* was 0.005 μg/ml or less. Concentrations of *M. pneumoniae* in bronchoalveolar lavage (BAL) were significantly lower in LBM-415-treated mice on days 6 and 13. Treatment with LBM-415 also decreased lung histopathological score, airways obstruction and airways hyperreactivity. Concentrations of proinflammatory and T-helper Th1 cytokines were significantly reduced in the BAL of LBM-415-treated mice. The study demonstrated the beneficial effect of LBM-415 on murine *M. pneumoniae*-induced pneumonia (23).

LBM-415 was also evaluated in other mouse models of infection, including lethal sepsis caused by MRSA and *S. pneumoniae*, thigh infection due to MRSA and pneumonia due to penicillin-sensitive *S. pneumoniae*. LBM-415 was active against both systemic MRSA and methicillin-susceptible *S. aureus*, with ED_{50} values of 2.5 and 2.3 mg/kg, respectively. Against these infections, its efficacy was comparable to linezolid and vancomycin. Against systemic penicillin-susceptible *S. pneumoniae* infection, the ED_{50} was 14.3 mg/kg. LBM-415 ED_{50} values for systemic multidrug-resistant *S. pneumoniae* infections were < 10 and 36.6 mg/kg following s.c. and oral administration, respectively. In the MRSA thigh infection model, bacterial burden was significantly reduced at 5.6, 16.7 and 50 mg/kg LBM-415 compared with controls, demonstrating comparable efficacy to linezolid. A dose of 23.3 mg/kg LBM-415 produced a 50% decrease in bacterial lung burden in the pneumonia model. The *in vivo* activity of LBM-415 in these models was evident irrespective of resistance to other antibiotics (24).

The effect of LBM-415 on the proteomes of *S. aureus* and *S. pneumoniae* has been investigated using 2-dimensional electrophoresis. The results showed that peptide deformylase inhibition by LBM-415 led to formylated peptide accumulation which, in the case of *S. pneumoniae*, was markedly time- and inhibitor concentration-dependent. The formylated peptides remained much longer in the presence of sub-MIC levels of LBM-415, correlating with the prolonged postantibiotic effect observed *in vitro* (8, 25).

Studies have been conducted to investigate mechanisms reducing the susceptibility of pathogens to LBM-415. Mutants of *S. aureus*, *S. pneumoniae* and *H. influenzae* with reduced susceptibility were selected by *in vitro* exposure to LBM-415. Representative isolates of *S. pneumoniae* had point mutations in the *defB* gene, but had no growth defects and no change in susceptibility to standard antibiotics. Mutations in the *fmt* gene were observed in isolates of *S. pneumoniae* and *H. influenzae*, with growth and morphological defects probably corresponding to impaired protein synthesis in the absence of formylation/deformylation. *H. influenzae* isolates show a wide range of susceptibilities to LBM-415, with MICs ranging from 0.06 to 32 μg/ml. *H. influenzae* isolates with mutations in the *acrR* gene have decreased susceptibility to macrolides. The impact of AcrAB efflux on susceptibility to LBM-415 was further investigated. Sequencing of the *acrR* gene in isolates less susceptible to LBM-415 indicated mutations in the published *acrR* sequence, with stops and frameshifts implying repressed pump expression. Consistent with this finding, inactivation of *acrR* in the *H. influenzae* strain NB65044 reduced the susceptibility to LBM-415 and other pump substrates. These studies indicated that repression of AcrAB-mediated efflux is a significant factor in decreased susceptibility to LBM-415 in *H. influenzae* (26, 27).

Pharmacokinetics and Metabolism

The pharmacokinetic profile of LBM-415 was investigated in rodents following single intravenous and oral doses. In a dose-ranging study, single oral doses of 11.9, 44.2, 124.2 and 436.2 mg/kg were administered to rats. LBM-415 was rapidly absorbed after oral administration in both mice and rats, with t_{max} occurring within 0.5 h for all doses. In mice, the oral bioavailability was 62.4%. In rats, the oral bioavailability ranged from 22 to 101%, with no saturation of absorption at higher doses. LBM-415 was rapidly distributed to all tissues studied. Saturation of

elimination appeared to occur at higher doses, but 24 h after all doses serum concentrations were low, with no evidence of accumulation. In rats, the majority of the compound was excreted in urine and bile in the unchanged form (28).

The pharmacodynamic properties of LBM-415 were investigated in studies using the neutropenic mouse thigh infection model. In time-course studies, single oral doses of LBM-415 were administered 2 h postinfection with *S. pneumoniae* strain NB07011. A dose of 320 mg/kg was cidal, while 80 mg/kg produced a bacteriostatic effect for up to 6 h. A pronounced postantibiotic effect of between 4.1 and 11.6 h was observed. In fractionated dosing studies, bacterial levels of *S. pneumoniae* in thighs were correlated with PK/PD indices and showed that AUC/MIC was the dominant parameter and correlated best with efficacy (29).

In further studies using mouse models of infection with *S. pneumoniae* and *S. aureus*, linear kinetics were observed with doses of LBM-415 from 20 to 320 mg/kg. Oral bioavailability was 67-88%. *In vivo* postantibiotic effects were 3-5 h with *S. aureus* and 10-13.5 h with *S. pneumoniae*, and AUC/MIC was highly correlated with efficacy. In normal and neutropenic mice infected with various pathogens, including MRSA and penicillin-, macrolide- and tetracycline-resistant strains of *S. pneumoniae*, the magnitude of the 24-h AUC/MIC required for *in vivo* efficacy did not vary significantly among strains. The presence of neutrophils reduced the AUC/MIC required for efficacy by approximately 4-fold (30, 31).

The single- and multiple-dose pharmacokinetics of LBM-415 were evaluated in human subjects. Single ascending doses of 100-3000 mg or multiple doses of 250, 500 and 1000 mg twice daily for 11 days (9-10 subjects per dose group) were administered. LBM-415 was rapidly absorbed, with the mean t_{max} ranging from 1 to 1.75 h across all dose groups. Pharmacokinetics were linear and no accumulation was observed in the multiple-dose study. The overall systemic exposure to the drug was not affected by food intake. The pharmacokinetic profile of LBM-415 supported a twice-daily dosing regimen (32).

LBM-415 is advancing into phase II/III clinical trials (33).

Sources

Novartis AG (CH); Vicuron Pharmaceuticals, Inc. (US).

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