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MEETING REPORT

HIGHLIGHTS FROM THE 50TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY (ICAAC)

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SUMMARY

The 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) was held on September 12-15, 2010, in Boston, once again providing a widely attended, broad-ranging congress covering all aspects of understanding and treating infectious diseases. Highlights of the meeting were easy to identify and are summarized below, focusing on advances in the development of drugs, vaccines and other therapeutic strategies for viral, bacterial and fungal infections and malaria, and on new molecular entities.

INTRODUCTION

This year, the American Society for Microbiology offered the 50th edition of the Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Boston. Much has changed in drug development, infectious diseases and microbiology since the first edition in 1961 –in fact, much has changed since 2009. In order to stay abreast of the latest innovations in the rapidly changing field of therapeutics for infectious diseases, we have selected presentations on promising pharmacological agents and other therapies under investigation. These are summarized below to provide the most up-to-date information available on their progress. Data on well-known and more recently identified agents are described, with the very latest compounds discussed in a section on new molecular entities.

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ANTIVIRALS

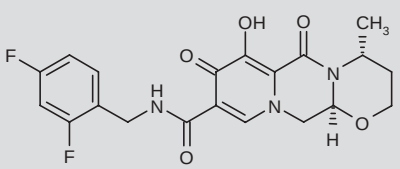
HIV

Among presentations related to HIV infection were those by investigators at Shionogi, GlaxoSmithKline and ViiV Healthcare, who described studies of the next-generation, oral, unboosted HIV integrase inhibitor **S/GSK-1349572**. The studies added to data on the agent's safety, pharmacokinetics and binding, and provided information on the effect of polymorphisms in the genetic information encoding HIV-1 integrase on the enzyme's susceptibility to the inhibitor.

Two HIV-1 integrase/DNA models were used to investigate the slower dissociation of S/GSK-1349572 versus raltegravir from wild-type integrase and the integrase mutants Q148, N155 and Y143. The experiments showed that structural characteristics of S/GSK-1349572 could explain the more favorable interactions of S/GSK-1349572 with wild-type and mutant integrase (1).

In vitro passaging of HIV-1-infected cells with S/GSK-1349572 has resulted in amino acid substitutions in HIV-1 integrase. Nonetheless, genetic polymorphisms at positions 101 and 124 caused no shift in fold change susceptibility of the enzyme to S/GSK-1349572 in vitro, and S/GSK-1349572 therapy led to robust anti-HIV-1 responses in a phase IIa trial in patients with and without those genetic polymorphisms (2).

In a randomized, single-dose, placebo- and moxifloxacin-controlled, crossover study in 42 healthy volunteers, a supratherapeutic dose of a S/GSK-1349572 suspension (250 mg) had no effect on cardiac



S/GSK-1349572

repolarization. The compound was generally well tolerated, with the most common adverse event being nausea in S/GSK-1349572-treated subjects, few adverse events above grade 1 and no safety signals in clinical laboratory values, vital signs or ECG readings (3).

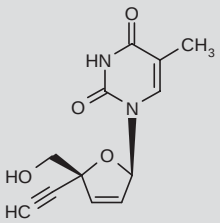
Dose adjustment of S/GSK-1349572 does not appear to be necessary with proton pump inhibitor coadministration. This was shown in an open-label study in healthy men who were given a single 50-mg dose of S/GSK-1349572, followed by a second treatment period in which they received omeprazole 40 mg once daily for 5 days, in addition to 50 mg S/GSK-1349572 on day 5. All treatments were given under fasted conditions. One drug-related adverse event (headache) was noted in subjects given S/GSK-1349572 alone and two (abdominal pain and dyspepsia) occurred in individuals given omeprazole and S/GSK-1349572. Coadministration of the agents had no effect on the pharmacokinetics of single-dose S/GSK-1349572 in plasma (4).

Phase II data were presented showing the efficacy of Gilead Sciences' Quad anti-HIV regimen. Data from the study revealed a high rate of virologic suppression through 48 weeks with the single-tablet regimen of elvitegravir (EVG), cobicistat (COBI; GS-9350), emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) (Quad; EVG/COBI/FTC/TDF). Additional phase II data showed the benefit of COBI-boosted atazanavir sulfate given in combination with Truvada® (FTC/TDF).

In the randomized, double-blind, multicenter Quad 236-0104 study, EVG/FTC/TDF/COBI was compared with efavirenz/FTC/TDF (Atripla™) in treatment-naive individuals with HIV infection. At 48 weeks, the primary objective (HIV RNA levels < 50 copies/mL) was achieved by 90% of the participants in the EVG/FTC/TDF/COBI group and by 83% of the subjects receiving efavirenz/FTC/TDF when missing values were counted as failures. When missing values were excluded, the respective values were 96% and 95%. The mean increase in $CD4^+$ T-cell counts were 240 and 162 cells/mm^3 in the EVG/FTC/TDF/COBI and efavirenz/FTC/TDF cohorts, respectively. Discontinuation, adverse event and grade 2-4 laboratory abnormality rates were similar in both groups.

Study 216-0105 compared COBI-boosted atazanavir and ritonavir-boosted atazanavir, both given with FTC/TDF, in treatment-naive patients with HIV infection. At 48 weeks, the primary objective (HIV RNA levels < 50 copies/mL) was achieved by 82% and 86% of the subjects, respectively, in the COBI and ritonavir arms in an analysis where missing equaled failure. The respective figures were 91% and 96% when missing values were excluded. Mean $CD4^+$ T-cell count increases were 230 and 206 cells/mm^3, respectively, in the COBI and ritonavir groups. Discontinuation and grade 2-4 laboratory abnormality rates were similar between the treatment cohorts. Increases in serum creatinine and decreases in creatinine clearance seen at early time points in the COBI arm stabilized through week 48 and were similar to changes in the ritonavir group. The mean decline in estimated glomerular filtration rate at 48 weeks was 13.3 mL/min in the COBI cohort and 13.8 mL/min in the ritonavir arm (5, 6).

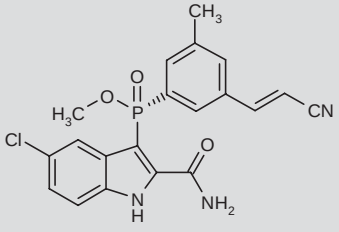
OBP-601 (**festinavir**; Oncolys BioPharma), a nucleoside reverse transcriptase inhibitor that previously exhibited safety and tolerability at single oral doses of up to 900 mg in healthy volunteers, is currently under evaluation in patients with HIV-1 infection. Results from



Festinavir

a phase Ib/IIa study of OBP-601 administered as monotherapy to treatment-experienced HIV-infected subjects were disclosed at this year's congress. In a double-blind, placebo-controlled, dose-ascending trial, individuals with HIV-1 infection who had received prior anti-HIV therapy but were off treatment at the time of study initiation received OBP-601 at doses of 100, 200, 300 and 600 mg once daily (n = 6/cohort) or placebo (n = 2/cohort) for 10 days. Safety analysis revealed adverse events in 4, 4, 2, 5 and 1 subjects, respectively, in the groups receiving placebo and 100, 200, 300 and 600 mg OBP-601. Two serious adverse events (septicemia and primary cytomegalovirus infection) were seen in patients treated with the 600-mg dose of OBP-601. Both adverse events were described as unrelated to the drug. Decreases in the levels of HIV RNA from baseline of −0.87, −0.98, −1.36 and −1.22 log copies/mL, respectively, were observed in subjects treated with OBP-601 at doses of 100, 200, 300 and 600 mg compared with −0.07 log copies/mL seen in the placebo group. The maximum tolerated dose (MTD) was not reached in this study. The findings support further evaluation of OBP-601 for the treatment of HIV-1 infection (7).

IDX-899 (GSK-224876, IDX-12899), a non-nucleoside reverse transcriptase inhibitor with anti-HIV potential, was initially developed by Idenix Pharmaceuticals and licensed last year to GlaxoSmithKline. Since a dose–response was not identified in an initial proof-of-concept study, an extension was designed with a dose of 30 mg given once daily for 7 days to HIV-1-infected patients who had not received antiretroviral therapy. Both randomized, double-blind and placebo-controlled studies showed IDX-899 to be well tolerated, with no drug-related adverse events, serious adverse events, deaths or adverse events leading to discontinuation. Headache, dyspepsia and nausea were the most common adverse events, and all adverse events were mild. In the initial study, doses of 100, 200, 400 and 800 mg once daily were associated with mean viral load reductions



IDX-899

of 1.8-1.9 log_{10} HIV-1 RNA copies/mL in plasma from baseline to day 8, while this reduction was 0.97 log_{10} HIV-1 RNA copies/mL with the 30-mg regimen. IDX-899 pharmacokinetics increased greater than dose proportionally at 30-100 mg once daily, dose-proportionally at 100-400 mg and less than dose proportionally at 400-800 mg once daily. The extension study allowed characterization of the relationship between viral load and pharmacokinetics (8).

A study in 24 healthy subjects using three metabolic probe drugs, midazolam, dextromethorphan and flurbiprofen, showed IDX-899 to be a weak inhibitor of cytochrome P450 3A4 and 2D6, and to have no effect on cytochrome P450 2C9. Low drug interaction potential was seen when IDX-899 was coadministered with the antiviral combinations lopinavir/ritonavir and darunavir/ritonavir; ritonavir-boosted protease inhibitors increased the exposure to IDX-899 < twofold. The agent was well tolerated in this study (9).

First-in-human data were disclosed on the anti-HIV-1 agent **NIBR-6465** (Novartis), an inhibitor of chemokine CCR2 and CCR5 receptors. Seven ascending single doses of NIBR-6465 (0.5, 1, 3, 10, 30, 100 and 200 mg) were administered to 56 healthy subjects (n = 8/cohort) in a randomized, double-blind, placebo-controlled study. The AUC and C_{max} for doses of 30, 100 and 200 mg increased in a non-dose-proportional manner, with respective terminal elimination half-life values of 623, 685 and 990 h. Dose-related gastrointestinal adverse events were reported in 14.3% of subjects across all cohorts. No significant safety concerns were raised in the study (10).

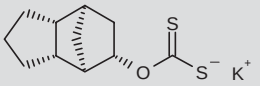
Pharmacokinetic/pharmacodynamic modeling was performed using data from evaluable whole blood concentrations and receptor occupancy profiles obtained from 18 participants treated at doses > 30 mg. A direct-effect three-parameter (E_0, E_{max} and EC_{50}) sigmoid E_{max} model with a baseline offset provided the best statistical fit for the data. Receptor occupancy of ≥ 90% for both CCR2 and CCR5 receptors was seen at doses of 30, 100 and 200 mg (11).

Influenza

The nanoemulsion-adjuvanted Fluzone® nasal influenza vaccine **NB-1008** (NanoBio) was well tolerated in a phase I study. In a randomized trial in 199 healthy volunteers, a single intranasal dose of NB-1008 was administered as a 5, 10, 15 or 20% oil-in-water emulsion with 12 or 30 µg total hemagglutinin (Fluzone®) in a total volume of 200 or 500 µL. Other subjects received NB-008, phosphate-buffered saline, intranasal Fluzone® or intramuscular Fluzone®. No significant adverse events or safety concerns were reported and NB-1008 elicited mucosal and systemic immunity; 10% NB-1008 with 30 µg total hemagglutinin was associated with > 2.5-fold increases in geometric mean titers and > 40% seroconversion for all three influenza strains in the vaccine. Nasal washing revealed a > twofold increase in influenza IgA titers (12).

Herpes

LMV-601 (Lumavita, Deutsches Krebsforschungszentrum) demonstrated potent activity against herpes simplex virus (HSV) and human papillomavirus (HPV) in preclinical studies. The agent, the (–)-enantiomer of the *exo,exo*-diastereomer of D-609, a mixture of four racemic diastereomers, represents the lead compound in a new class of drugs that act as inhibitors of phosphatidyl choline-specific



LMV-601

phospholipase C (PC-PLC) by blocking both the replication of viral DNA and the expression of viral genes. The agent is currently under phase I clinical development for the treatment of HSV infections. LMV-601 was reported to be approximately fourfold more active at inhibiting PC-PLC and was more potent at suppressing the replication of HSV-2 than the (+)-*exo,exo*-enantiomer. The compound also displayed a twofold higher therapeutic index (estimated as the ratio of cytotoxicity [LD_{50}] over the inhibition of HSV-2 [IC_{50}]) than the *exo,exo*-racemate and the (+)-enantiomer (13).

In HSV-2-infected BALB/c mice, topical treatment with LMV-601 suspended in a hydrocarbon ointment base (1.25%, 1.875% and 2.5% w/w) twice daily for 10 days was well tolerated and dose-dependently improved symptoms versus vehicle control (14).

LMV-601 also exhibited antiviral activity against HPV types 16, 18 and 31 in human cervical carcinoma cells and reduced the expression of virus-specific E7 mRNA (> 50-fold at 40 µg/mL and approximately 1,000-fold at ≥ 80 µg/mL) (15).

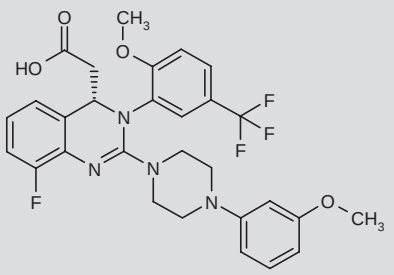
PP-9706642 (Piramal Life Sciences), a hydromethanolic extract derived from the roots of *Indigofera heterantha*, showed promise as a prophylactic/therapeutic agent for HSV-2 infection in a preclinical study. In vitro PP-9706642 displayed antiviral activity in cytopathic and MTT assays and in a plaque reduction assay in Vero cells infected with HSV-2. The agent was shown to suppress the proliferation of HSV-2 in MTT and plaque reduction assays in a concentration-dependent manner (IC_{50} = 33.5 µg/mL; CC_{50}/IC_{50} = 13). A single topical intravaginal prophylactic administration of a cream formulation of PP-9706642 (125 mg/kg) correlated with 100% survival of BALB/c mice that were subsequently infected with HSV-2. Therapeutic dosing of the agent at 375 mg/kg/day given at several time points following infection of BALB/c mice with HSV-2 resulted in survival rates of 70-100%. A significant decrease in the viral titer was seen in vaginal lavage samples collected from PP-9706642-treated mice compared with values in untreated animals or those in the placebo group (16).

Cytomegalovirus

Presentations dealing with other kinds of viral infections included one showing that the **TransVax™ vaccine** reduces cytomegalovirus (CMV) viremia. The ability of TransVax™ vaccine to limit CMV reactivation in patients undergoing hematopoietic stem cell transplantation was evaluated in a double-blind phase II study including 80 immunosuppressed CMV-seropositive patients randomized to placebo or 4 doses of the vaccine. The participants received treatment 3-5 days before and approximately 1, 3 and 6 months after the transplant. The vaccine was well tolerated, with one patient discontinuing due to an adverse event possibly related to the study vaccine, and a similar number of serious adverse events between treatment

groups in the intent-to-treat population after 1 year of follow-up. In comparison with values in the group receiving placebo, the levels of antibodies targeting glycoprotein B were increased in the vaccinated cohort, as were the numbers of T cells specific for CMV envelope glycoprotein B (gB) and 65-kDa phosphoprotein (pp65) up to 1 year. In the per-protocol population, detectable CMV viremia was noted in 32% of TransVax™-treated subjects and in 62% of those receiving placebo. In the TransVax™ cohort, initial viremia also occurred later and the number of CMV viremia episodes was significantly lower, as was the duration of viremia (mean duration of 10.6 days vs. 19.5 days, respectively, for TransVax™ and placebo). Endpoints relating to the initiation and duration of CMV-specific antiviral therapy did not show a significant difference between groups in the per-protocol population, but the study size was underpowered for these assessments. Further development of the TransVax™ vaccine appears warranted (17). Vical's TransVax™ CMV vaccine has orphan drug status from the FDA for the prevention of CMV infection in individuals receiving hematopoietic stem cell and solid organ transplants who are at risk of such an infection.

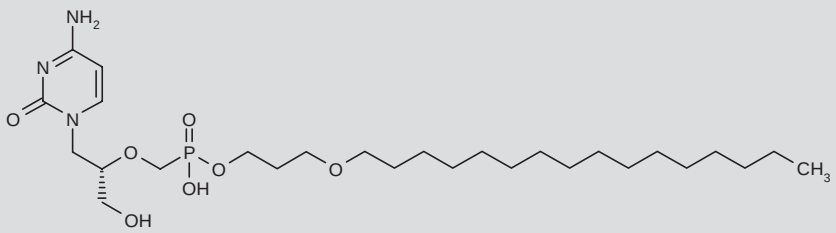
Favorable safety and pharmacokinetics were seen in phase I trials of **AIC-246** (AiCuris), a novel non-nucleoside compound that exhibits sustained activity against human CMV. In two double-blind, placebo-controlled, single-dose escalation studies (A and B) healthy male subjects received AIC-246 as solution (5-80 mg) or tablet (80-320 mg) formulation (n = 28 and 48, respectively), whereas 24 participants were given placebo. In trial C, an open-label, uncontrolled, two-period, crossover study, 11 male volunteers received AIC-246 (20-mg tablet) under fasted or fed (high-fat, high-calorie) conditions in each period. Trial D was designed as a double-blind, placebo-controlled, multiple dose-escalation study in which male and female participants (n = 6 in each cohort) were given placebo followed by AIC-246 (120, 180 and 240 mg b.i.d.) for 2 weeks. Pharmacokinetic profiling in trials A and B revealed a greater than proportional increase in the exposure of AIC-246 at doses up to 240 mg, with no further increase at higher dose levels (240-320 mg). The median t_{max} and mean terminal $t_{1/2}$ were estimated at 1.5 and 10 h, respectively. In trial C, the intake of food resulted in reductions in the rate and extent of absorption of the compound; the median t_{max} was calculated at 4 h and a decrease in C_{max} of 24% was reported in fed compared with fasted conditions. However, the $AUC_{(0\text{-inf})}$ remained unaffected by food consumption. Multiple-dose administration of AIC-246 in trial D had no impact on the mean terminal $t_{1/2}$ and median t_{max} values compared with single doses of the agent. Safety analysis indicated that treatment with AIC-246 did not correlate with the incidence of dose-dependent adverse events and no effects of the compound were observed on laboratory, vital sign and ECG parameters. Phase IIa data from patients who received kidney or kidney/pancreas transplants and were treated preemptively for 14 days with AIC-246 showed that the drug had good tolerability and efficacy comparable to that of valganciclovir (18). A randomized, double-blind, placebo-controlled, parallel-assignment phase II trial that aims to investigate the safety, tolerability and efficacy of AIC-246 in the prevention of CMV reactivations in patients with bone marrow transplants is currently recruiting participants. The estimated completion date for this study is May 2011 (19).



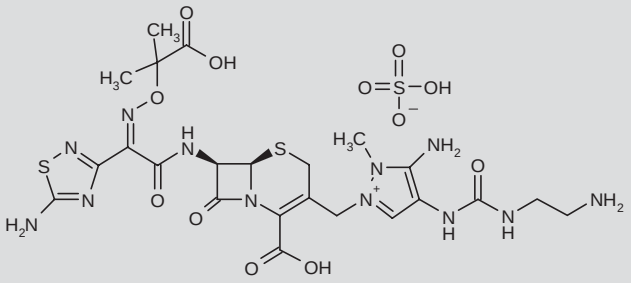
AIC-246

Other

Also presented were data indicating that **CMX-001** (hexadecyloxypropyl-cidofovir) is not nephrotoxic in patients with viral infections. Chimerix is developing the DNA polymerase inhibitor as a treatment for double-stranded DNA virus infections. The agent is meant to overcome the limitations of cidofovir, namely the requirement of in-hospital intravenous administration and the risk of nephrotoxicity. Nearly 100 patients severely infected with double-stranded DNA viruses (e.g., CMV, HSV, Epstein-Barr virus and JC virus) have received oral CMX-001 under emergency IND applications, with doses up to 4 mg/kg administered. Data from 46 participants (many of whom had severe renal impairment prior to CMX-001 treatment) revealed unchanged or improved renal function in most subjects. Systemic exposure to the compound was unaffected by moderate to severe renal impairment in pediatric and adult



CMX-001



CXA-101

patients and by hemodialysis. CMX-001 is also being evaluated in a phase II trial in stem cell transplant recipients who are seropositive for CMV and in a phase I study in transplant recipients with BK viruria (20, 21).

ANTIBIOTICS AND ANTIBACTERIALS

Several in vitro and in vivo studies characterized the activity of Cubist Pharmaceuticals' cephalosporin antibiotic **CXA-101** and data from a phase II trial in patients with urinary tract infection were also made available. The activity of CXA-101 was evaluated against a collection of 190 *Pseudomonas aeruginosa* isolates, which were recovered from bloodstream infections of participants in a multicenter study conducted in Spain in 2008 and who overexpressed prevalent genes leading to resistance. The agent was active against all 190 isolates and was only associated with MIC values > 8 mg/L against 2 isolates, which both produced metallo-β-lactamase VIM-2 (22).

A study of the impact of *P. aeruginosa* mutants overexpressing ampC, oprD and efflux pumps found that most resistance mechanisms did not affect susceptibility to CXA-101, unlike other β-lactams. Decreased susceptibility was only observed with some ampC-derepressed mutants (23).

A mouse peritonitis model was used to compare the activities of CXA-101 alone, CXA-101/tazobactam, ceftazidime and piperacillin sodium/tazobactam sodium against extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* strains. Tazobactam was not effective against the KP1 strain and did not add to the efficacy of CXA-101. Activity was similar with CXA-101/tazobactam and ceftazidime against the KP2 strain, and CXA-101/tazobactam was the only effective treatment against the highly resistant KP3 strain (24). The combination of CXA-101 and tazobactam is in phase II investigation at Cubist.

In a study using an immunocompetent murine thigh infection model, animals were infected with Gram-negative organisms and administered CXA-101 with or without tazobactam at doses designed to approximate the free time above the MIC seen in humans given 1 g of CXA-101 plus tazobactam every 8 h. When compared with animals given tazobactam at doses designed to approximate the free time above the MIC seen in humans given a 4.5-g dose every 6 h, CXA-101 treatment resulted in significant reductions in colony-forming units (CFU) in 9 of 16 isolates, and the addition of tazobactam to CXA-101 produced significant reductions in CFU in 10 of 16 isolates (25).

In a murine model of pneumonia caused by two *P. aeruginosa strains*, CXA-101 was more effective than tazobactam against both strains and more effective than ceftazidime against a highly virulent strain. Doses used were designed to approximate free drug AUC values obtained with i.v. formulations in humans (26).

A study in healthy adults found that i.v. administration of a fixed 2:1 ratio of CXA-101 (500, 1000 and 2000 mg) and tazobactam (250, 500 and 1000 mg) did not affect the pharmacokinetics of either agent or the active metabolite of tazobactam, M-1 (27).

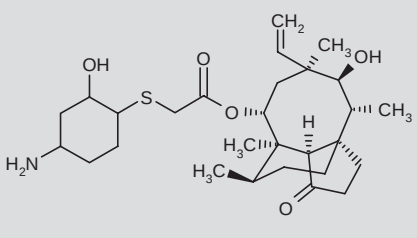
Finally, i.v. CXA-101 (1000 mg every 8 h) was compared to i.v. ceftazidime (1000 mg every 8 h) in patients with complicated urinary tract infections in a phase II study. The randomized, double-blind trial was conducted at multiple centers, with 129 patients enrolled. Treatment lasted 7-10 days. This first clinical study of CXA-101 conducted in patients found microbiologic cure rates of 83.1% and 76.3%, respectively, in the CXA-101 and ceftazidime groups in the microbiological intent-to-treat population, and rates of 85.5% and 92.6%, respectively, in the microbiologically evaluable population with a urine culture at 6-9 days post-therapy and adherence to the protocol. Lower cure rates in the latter population with CXA-101 may have been due to differences in populations, including a higher rate of *P. aeruginosa* infections in the CXA-101 cohort. The activity of the two agents was comparable in terms of clinical cure rates and in patients with complicated lower urinary tract infections and those with pyelonephritis. CXA-101 appeared to be safe and well tolerated, with adverse events similar between treatment groups (28).

Multiple presentations were given on Nabriva Therapeutics' pleuromutilin antibiotic **BC-3781**, which is in phase I development for community-acquired pneumonia and phase II testing for skin infections.

MIC_{90} values against organisms responsible for community-acquired respiratory tract infections (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae* and *Legionella pneumophila*) were 0.25-2 μg/mL with BC-3781 and were not affected by resistance to other agents (29).

When tested against 671 strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and 253 *S. aureus* strains susceptible to oxacillin (MSSA), most isolates were inhibited by ≤ 0.12 μg/mL BC-3781 and 99% were inhibited by ≤ 0.25 μg/mL BC-3781, with 4- to 16-fold greater potency than the next most potent agents tested (linezolid and vancomycin) (30).

Disk diffusion and MIC Clinical and Laboratory Standards Institute quality control guidelines were determined for BC-3781 against sev-



BC-3781

eral organisms. Proposed MIC quality control ranges against *H. influenzae* ATCC 49247, *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619 were 0.5-2 µg/mL (94.3% of total), 0.06-0.25 µg/mL (100% of total) and 0.06-0.5 µg/mL (93.6% of total), respectively. The proposed disk diffusion quality control ranges for *H. influenzae* ATCC 49247, *S. aureus* ATCC 25923 and *S. pneumoniae* ATCC 49619 were 22-28 mm (96.0% of total), 26-32 mm (97.4% of total) and 19-27 mm (99.3% of total), respectively (31).

In mouse models of bacteremia, BC-3781 was superior to linezolid and vancomycin, with ED_{50} values of 1.77 mg/kg/day against MSSA and 0.23 mg/kg/day against MRSA. Efficacy in a murine model of MRSA thigh infection was similar to that of s.c. vancomycin and linezolid after 2 days of treatment (32).

BC-3781 demonstrated efficacy against murine pulmonary infections caused by *S. pneumoniae* (dose required to reduce 1 $\log_{10}$ CFU/lung = 12.6 mg/kg/day vs. 28.3 mg/kg/day for moxifloxacin and 77.4 mg/kg/day for linezolid), *H. influenzae* (dose required to reduce 1 $\log_{10}$ CFU/lung = 76.1 mg/kg/day vs. 27.2 mg/kg/day for azithromycin) and MRSA (dose required to reduce 1 $\log_{10}$ CFU/lung = 53.7 mg/kg/day vs. 291 mg/kg/day for vancomycin and 108 mg/kg/day for linezolid), with excellent penetration into the epithelial lining fluid at a dose of 35 mg/kg (33).

In neutropenic murine thigh and lung infection models (*S. aureus*, MRSA, *S. pneumoniae*, penicillin-resistant *S. pneumoniae*), BC-3781 displayed time-dependent killing with moderate post-antibiotic effects of 1-3 h. The mean bacteriostatic free drug 24-h AUC/MIC ratio was 11.5 (34).

BC-3781 was safe and well tolerated in a randomized, double-blind, placebo-controlled study in which healthy subjects received single oral doses of 100, 200 or 400 mg and in a randomized, double-blind trial of the agent in which healthy individuals were given placebo or twice-daily doses of 200, 400 or 600 mg for 9 days, with a single dose on day 10. Rapid absorption and a half-life of approximately 10 h were noted, with steady state reached after the fifth dose and a large volume of distribution (35).

Lastly, healthy men (n = 12) and women (n = 12) aged 18-55 years and healthy elderly subjects (n = 12) participated in a randomized, double-blind, placebo-controlled study of BC-3781 given as a single dose of 150 mg i.v. Pharmacokinetics did not differ significantly by age or gender, renal excretion of BC-3781 was low and the drug was well tolerated in all groups. It was concluded that dose adjustment of BC-3781 based on age or gender was not required (36). The compound has been described in the patent literature (WO 2008113089).

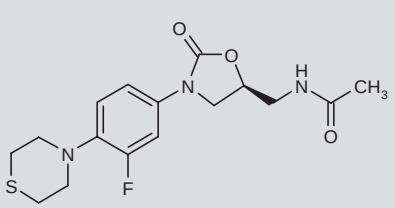
The linezolid analogue **PNU-100480**, in early clinical development at Pfizer as a treatment for tuberculosis, was well tolerated in healthy volunteers and its activity against resistant bacteria was demonstrated in vitro.

PNU-100480 (mean MIC = 0.12 mg/L) was more active against clinical multidrug-resistant *Mycobacterium tuberculosis* isolates than linezolid (mean MIC = 0.39 mg/L) (37).

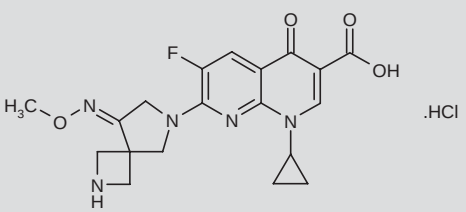
In 2 studies in healthy volunteers, 19 subjects received up to 2 escalating single oral doses of PNU-100480 (35-1500 mg) or placebo, while 8 subjects were given 4 daily doses of linezolid 300 mg. All PNU-100480 doses were safe and well tolerated; no serious adverse events or discontinuations occurred. Exposure to the parent drug and metabolites was approximately proportional to dose up to the 1000-mg dose. Bactericidal activity against *M. tuberculosis* was determined in whole blood bactericidal culture, revealing maximal activity with both PNU-100480 and linezolid at concentrations twice the MIC values, suggesting time-dependent killing. The maximal effect of linezolid, however, was less than one-half that of PNU-100480 (38).

In another study, healthy volunteers were randomized to placebo or PNU-100480 100, 300 or 600 mg b.i.d. or 1200 mg once daily for 14 days, linezolid 300 mg once daily for 4 days or PNU-100480 600 mg b.i.d. for 28 days. All doses of PNU-100480 were safe and well tolerated, and no safety signals related to inhibition of mitochondrial protein synthesis were observed during the 28 days of administration of PNU-100480 600 mg b.i.d. Adverse events were mild in intensity. Ex vivo whole blood culture studies showed superior cumulative bactericidal activity against *M. tuberculosis* with PNU-100480 compared to linezolid. With both agents, time-dependent bactericidal activity was seen and peaked at approximately twice the MIC, with the maximal effect of PNU-100480 more than double that of linezolid. The whole blood model also revealed synergy between PNU-100480 and pyrazinamide (39).

Treatment with the fluoroquinolone antibiotic **zabofloxacin hydrochloride** (DW-224a; Dong-Wha Pharmaceuticals) at either a therapeutic or supratherapeutic dose was not associated with clinically relevant effects on cardiac repolarization according to results reported from a recent phase I trial. The agent is currently undergoing phase II clinical development for the treatment of respiratory tract infections, particularly pneumonia. Male and female volunteers aged 18-45 years (N = 60) were randomized in a 1:1:1:1 ratio to receive zabofloxacin (400 [therapeutic dose] or 1500 mg [supratherapeutic dose]), moxifloxacin (400 mg) or placebo in a triple-blind, triple-



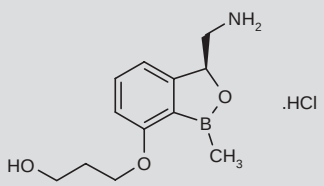
PNU-100480



Zabofloxacin hydrochloride

dummy, 4-way crossover trial. The study's primary objective was to assess the effects of zabofloxacin on cardiac repolarization using the baseline and placebo-adjusted time-matched analysis of each participant's individually corrected QT (QT_c) interval prolongation. Secondary objectives included quantification of the relationship between the zabofloxacin concentration in the plasma and changes in the subject's individual QT_c interval, as well as assessments of the agent's safety and tolerability. A total of 50 participants completed the trial. Treatment with zabofloxacin did not affect the heart rate, PR and QRS intervals or the waveform morphology of the ECG. The most common treatment-emergent adverse events seen in > 5% of subjects included contact dermatitis, dizziness, headache, nausea and vomiting. No serious adverse events occurred and no safety concerns were raised based on measurements of laboratory parameters, ECG and vital signs (40).

A number of antibacterial agents with a variety of other mechanisms of action were presented at the congress. Among these was **AN-3365** (GSK-2251052; Anacor Pharmaceuticals, GlaxoSmithKline), a boron-containing small molecule that features a new mechanism of action linked to potent activity against Gram-negative bacterial infections. AN-3365 acts by inhibiting bacterial leucyl-tRNA synthetase, the enzyme that catalyzes the attachment of leucine to its cognate transfer RNA (tRNA) molecule, via a novel mechanism of action described as oxaborole tRNA trapping (OBORT). The boron atom of AN-3365 interacts with the editing domain of leucyl-tRNA synthetase, forming an adduct with the terminal adenosine ribose moiety of the leucine-bearing tRNA molecule, causing the molecule to be trapped on the enzyme, and thus blocking protein synthesis. The agent was shown to exhibit an IC_{50} of 0.31 μM for inhibition of leucyl-tRNA synthetase (41).



AN-3365

Evaluation of the activity of AN-3365 in vitro against wild-type and multidrug-resistant (MDR) *Enterobacteriaceae* revealed a log-normal distribution with an MIC of 0.5 μg/mL for all bacterial species tested except *Proteus mirabilis* (MIC = 1 μg/mL). AN-3365 was described as more potent than the active comparators tigecycline, imipenem and cefepime (respective MIC_{90} values of 1, 2, 2 and 4 μg/mL) and did not appear to be affected by the presence of mechanisms associated with resistance to β-lactams (42).

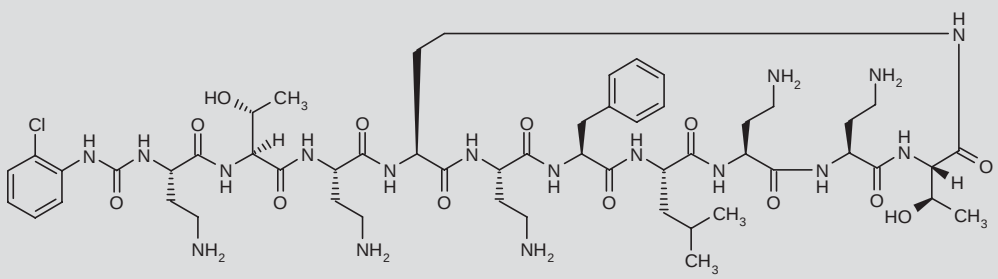
AN-3365 displayed sustained antimicrobial activity against MDR isolates of *P. aeruginosa* (MIC_{50} = 4 μg/mL; MIC_{90} = 8 μg/mL) and exhibited higher potency than nine comparators, including gentamicin, imipenem, levofloxacin and tigecycline (43).

When tested against 125 Gram-negative and Gram-positive anaerobic clinical pathogens and against 28 *Neisseria gonorrhoeae* isolates, AN-3365 displayed potent in vitro activity against all anaerobic bacteria at concentrations ≤ 2 μg/mL and inhibited the growth of ciprofloxacin-resistant *N. gonorrhoeae* isolates (44).

Pharmacokinetic profiling of AN-3365 in CD-1 mice following administration at 30 mg/kg s.c. revealed good exposure ($AUC_{[last]}$ = 12.1 h.μg/mL) with a terminal half-life of 2.5 h and a bioavailability of 100%. In CD-1 mice with cyclophosphamide-induced neutropenia, a single dose of AN-3365 30 mg/kg s.c. prevented the growth of MDR *Escherichia coli* ESBL strains and the *P. aeruginosa* ATCC 27853 strain, exhibiting respective log_{10} reductions in CFU of 3.04 and 4.94 compared with vehicle-treated controls at 24 h. The findings support the additional evaluation of AN-3365 as an antibacterial therapeutic (45). AN-3365 has been described in the patent literature (WO 2008157726; WO 2010080558).

Numerous studies of the polymyxin derivative **CB-182804** (Cubist Pharmaceuticals, BioSource Pharm), in early-phase clinical development as a therapy for Gram-negative bacterial infections, were detailed. CB-182804 was active in vitro against multidrug-resistant *Acinetobacter baumannii*, *E. coli*, *K. pneumoniae* and *P. aeruginosa*, with a spectrum and potency similar to that of polymyxin B. Efficacy greater than that of colistin and similar to that of ciprofloxacin was seen in a *P. aeruginosa* murine model of septicemia (46).

Experiments in *E. coli* indicated that CB-182804 binds to lipopolysaccharide and has a membrane-active mechanism of action similar to that of polymyxin B (47).



CB-182804

Against stock isolates with known resistance, CB-182804 was associated with MIC_{50} values of ≤ 1 µg/mL against *A. baumannii*, ESBL$^+$ *E. coli*, ESBL$^+$ *K. pneumoniae*, carbepenem-hydrolyzing β-lactamase KPC (KPC)-producing (KPC$^+$) *K. pneumoniae* and drug-resistant *P. aeruginosa*; MIC_{90} values were elevated against the latter two strains (48).

CB-182804 displayed excellent activity against Gram-negative pathogens (*E. coli*, *Enterobacter* spp., *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*) collected in New York City in 2009, with MIC values lowered by the addition of rifampin (49).

MIC values associated with CB-182804 were 0.5-2.0 µg/mL against Gram-negative rods (*E. coli*, *Enterobacter cloacae*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*), with good time-kill activity also seen against susceptible and resistant rods (50).

Resistance index testing using Gram-negative isolates showed values to be similar for CB-182804 and polymyxin B, although some strains had a significantly higher CB-182804 resistance index. CB-182804 appeared to share a mechanism of resistance with other polymyxins (51).

Against 455 clinical strains of Gram-negative pathogens, CB-182804 had in vitro activity and a spectrum similar to that of colistin, including colistin-susceptible strains that were resistant to all other currently available antimicrobials for clinical use (52).

CB-182804 was effective in vivo against Gram-negative pathogens (including multidrug-resistant strains) in a mouse model of septicemia, as well as in models of thigh and lung infection (both in mice and rats). The agent's efficacy was similar to that of polymyxin B (53).

Dose-dependent bactericidal efficacy (> 3 log_{10} reduction in CFU) was seen against *P. aeruginosa* in a neutropenic murine pneumonia model. Distribution of the compound into epithelial lining fluid and lung tissue was observed. Dose fractionation studies also indicated that the AUC/MIC ratio was the primary driver of efficacy (54).

Single i.v. doses of CB-182804 resulted in excellent systemic exposures in rats, mice and monkeys, with the highest exposure in monkeys and exposure higher in male versus female monkeys. A dose-proportional response in systemic exposure was seen when the dose was increased in monkeys (55).

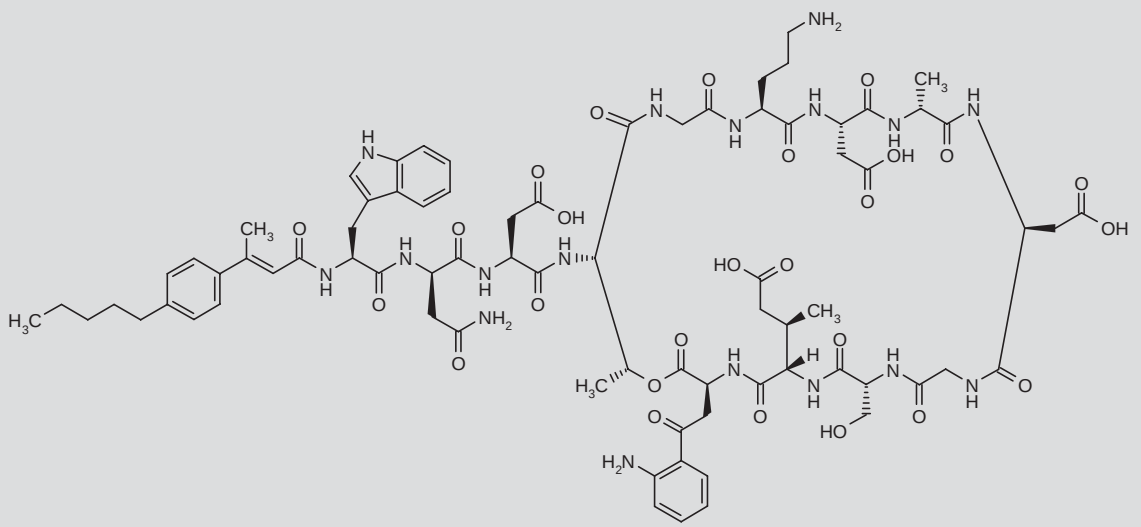
When evaluated in female cynomolgus monkeys, nephrotoxicity was reduced with CB-182804 versus polymyxin B on a dose-normalized basis at the clinically relevant polymyxin B dose regimen of 37,500 IU/kg/dose given i.v. twice daily for 7 days. The no observed adverse effect level of CB-182804 in monkeys treated for 7 days either two or three times daily was 75,000 IU/kg/day i.v. Renal pathology at that dose was mild (56).

Preclinical and clinical data were provided for the cyclic lipopeptide **CB-183315** (Cubist Pharmaceuticals), which is being developed as a therapy for diarrhea caused by *Clostridium difficile* infection (CDI). Structure–activity relationship (SAR) studies of daptomycin tail analogues led to the discovery of CB-183315, which was associated with MIC_{90} values of 0.5-1 µg/mL against *C. difficile* in vitro and protected hamsters against *C. difficile* infection when administered daily for 5 days at doses of 0.5 mg/kg by oral gavage (57).

Determination of the in vitro activity of CB-183315 against *C. difficile* and other enteric anaerobic and facultative organisms indicated that CB-183315 could be used to treat CDI without disrupting normal gut colonization (58).

In vitro activity was seen with CB-183315 against *S. aureus*, including clinical methicillin-resistant and -susceptible strains varying in their production of staphylococcal enterotoxin, with activity maintained under anaerobic conditions as an estimate of activity in the context of colitis (59).

Against metronidazole-resistant *C. difficile* isolates or *C. difficile* iso-



CB-183315

lates associated with vancomycin MIC values of 4 µg/mL, CB-183315 MIC values were ≤ 0.125 µg/mL. Activity against other Gram-positive anaerobic bacteria was also seen (60).

The mechanism of action of CB-183315 appeared to be similar to that of daptomycin (membrane depolarization) in studies using *S. aureus*. Further study indicated that the emergence of resistance in *C. difficile* would be low and showed that the postantibiotic effect of CB-183315 at a concentration eightfold the MIC was relatively short (0.9 h) (61).

CB-183315 demonstrated efficacy similar to matched doses of vancomycin in a hamster model of CDI, both in preventing initial disease onset and in terms of recurrence rates (62).

Lastly, analysis of stool samples from 30 subjects enrolled in a phase I trial showed that CB-183315 at doses of 0.5, 1.0 and 2.0 g b.i.d. did not have a large effect on fecal flora (63).

Colonization with nontoxigenic *C. difficile* (NTCD) may be a means of protecting against *C. difficile* infection, a possibility under investigation with the development of **VP-20621** (ViroPharma). Healthy volunteers age 60 years and older were treated for 5 days with vancomycin 125 mg and then with either once-daily VP-20621 (oral suspension containing 1 x 10^4, 1 x 10^6 or 1 x 10^8 spores) or placebo for 14 days. No serious or severe adverse events occurred and no VP-20621 discontinuations due to adverse events were reported. Gastrointestinal adverse events were observed in 22% of subjects given VP-20621 and in 33% of those given placebo; mild loose or watery stool not requiring treatment was reported on a single day by three individuals given VP-20621. All VP-20621-treated subjects had stool cultures positive for nontoxigenic *C. difficile* by day 6, while none tested positive for toxin-producing strains of *C. difficile* during the 28-day study period. Among placebo-treated subjects, five of nine (56%) tested positive for either toxin-negative or -positive *C. difficile* during the study period. The ability of VP-20621 to reduce the incidence of recurrent disease in patients with *C. difficile* infection is to be evaluated in a phase II study (64, 65).

Available results make possible a detailed overview of the development to date of GlaxoSmithKline's peptide deformylase (PDF) inhibitor **GSK-1322322**, an antibacterial agent that has entered phase I/II development for skin infections and pneumonia. To target PDF, pyrimidine ring SAR analyses were conducted, leading to the selection of a hydrazinopyrimidine series of PDF inhibitors and GSK-1322322 as a clinical candidate. The agent was associated with MIC_{90} values of 1 µg/mL against *S. pneumoniae* isolates, 4 µg/mL against *H. influenzae* isolates and 4 µg/mL against MRSA, and displayed oral bioavailabilities of 91%, 75% and 16%, respectively, in rats, dogs and monkeys (66).

Proposed MIC quality control ranges for GSK-1322322 were 1-4 µg/mL against *S. aureus* ATCC 29213, 0.5-4 µg/mL against *H. influenzae* ATCC 49247 and 0.12-0.5 µg/mL against *S. pneumoniae* ATCC 49619 (67).

GSK-1322322 and two other PDF inhibitors inhibited *S. aureus* growth at or below concentrations eightfold lower than the MIC after 6- to 8-h incubation by two different methodologies, an effect not seen with antibiotics with a different mechanism of action (68).

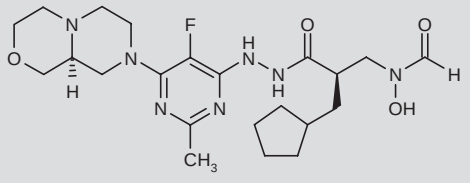
The agent was also evaluated for its in vitro activity against 4,836 recently collected common skin and soft tissue infection and respiratory tract pathogens, including resistant strains. It was associated with MIC_{90} values of 4 µg/mL against *S. aureus*, 0.5 µg/mL against *Streptococcus pyogenes*, 1-2 µg/mL against *S. pneumoniae*, 4-8 µg/mL against *H. influenzae* and 1-2 µg/mL against *M. catarrhalis* strains (69).

In an abscess infection model of MRSA infection, GSK-1322322 given orally b.i.d. for 4 days demonstrated excellent activity, reducing the CFU count per abscess by 3.9 $\log_{10}$ at 75 mg/kg when tested against the multidrug-resistant A-24 strain, by 3.3 $\log_{10}$ at 37.5 mg/kg when tested against the T5887 strain and by 2.6 $\log_{10}$ at 37.5 mg/kg when tested against the Panton-Valentine-positive strain of MRSA (70).

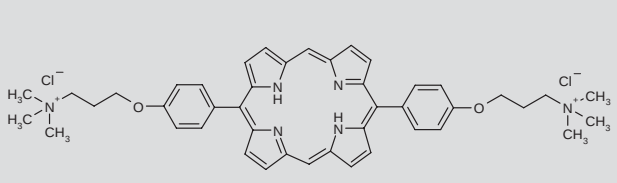
Potent in vivo activity was seen with GSK-1322322 given orally twice daily for 4 days in a rat respiratory tract infection model. The compound reduced the CFU count of the macrolide-resistant *S. pneumoniae* Ery-2 strain by 2.7 $\log_{10}$ at 37.5 mg/kg and that of *H. influenzae* by 2.9 $\log_{10}$ at 75 mg/kg (71).

Resistant *S. aureus* strains were used in an abscess infection model in rats, in which an oral controlled-infusion system recreated human single-dose exposure profiles of 1000 and 1500 mg b.i.d. GSK-1322322 and comparator antibiotics. The GSK-1322322 exposure profiles were highly effective against the three tested *S. aureus* isolates, with reductions in CFU/abscess of 3.1-3.8 $\log_{10}$ with the recreated 1000-mg dose and 2.5-2.9 $\log_{10}$ with the recreated 1500-mg dose (72).

The first-in-human study of GSK-1322322 evaluated single fasted doses of 100, 200, 400, 800 and 1500 mg, and also assessed the administration of 800 mg GSK-1322322 with food. The randomized, double-blind, placebo-controlled trial included 33 healthy volunteers. The agent was generally well tolerated, with headache the most common drug-related adverse event. No adverse events led to withdrawal. Drug exposure increased with dose between the 100- and 1500-mg doses. Repeated dosing in healthy subjects and patients is currently being studied (73).



GSK-1322322



XF-73

The novel porphyrinic antibacterial agent **XF-73** is being developed by Destiny Pharma for nasal decolonization of *S. aureus* and bacterial skin infections. In a phase I trial in healthy subjects with confirmed nasal *S. aureus* (N = 45), placebo or XF-73 (37.5, 75 or 150 µg b.i.d.) was administered in both nostrils for 5 days. All XF-73 doses were well tolerated; mild adverse events occurred in 8 of the 36 participants receiving XF-73 versus 3 of the 9 receiving placebo, and mild nasal adverse events occurred in 1 subject treated with 75 µg XF-73 b.i.d. and in 1 participant receiving placebo. Laboratory parameters, ECG and vital signs were not significantly affected by the agent and no systemic absorption of XF-73 was detected. The two highest XF-73 doses were associated with reductions in *S. aureus* colonization. The 150-µg XF-73 dose was associated with scant or absent colonization in all treated subjects after 5 days and with absent colonization at the end of treatment in six (55%) of the participants receiving it (74).

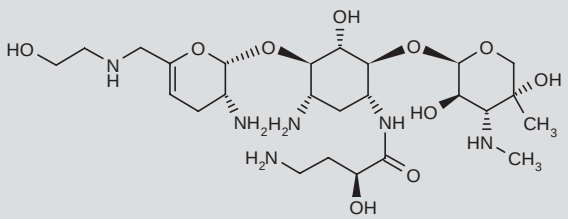
Multiple studies were presented describing the in vitro activity, pharmacokinetics and clinical safety of **ACHN-490**, a next-generation aminoglycoside under development at Achaogen.

E. coli and *K. pneumoniae* isolates were collected from 16 hospitals in New York City, and > 99% of isolates from each group were inhibited by 2 µg/mL ACHN-490, including aminoglycoside-resistant isolates and KPC+ *K. pneumoniae* isolates. The activity of ACHN-490 was not reduced by common aminoglycoside-modifying enzymes (75).

When tested against *P. aeruginosa* isolates, ACHN-490 demonstrated synergy with cefepime, doripenem and piperacillin/tazobactam against ≥ 90% strains at 12 and 24 h (76).

Against 493 recently collected clinical isolates of MRSA from U.S. hospitals, ACHN-490 was more active than amikacin and tobramycin and had similar activity as gentamicin, with an MIC_{90} of 2 µg/mL (77).

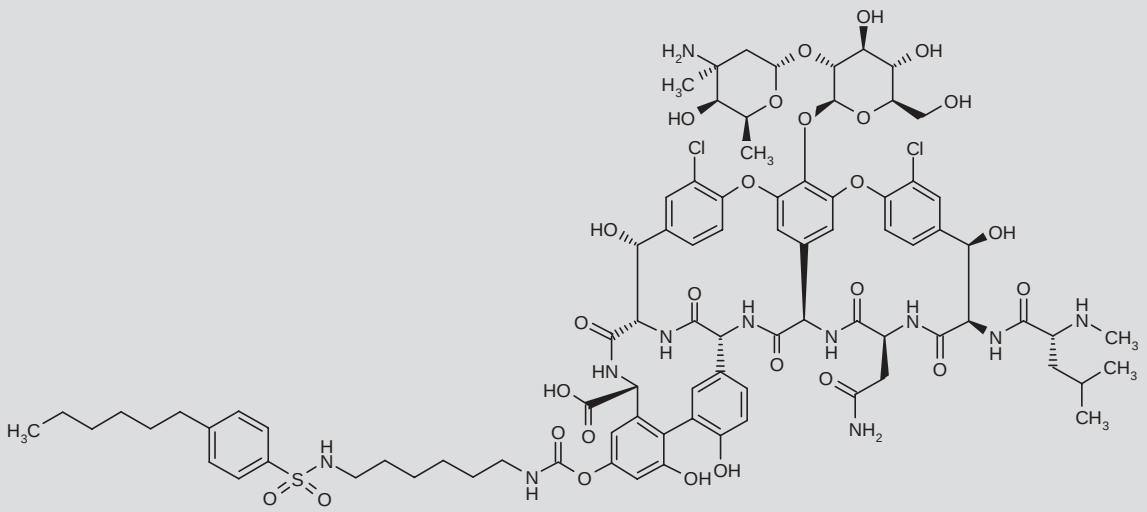
ACHN-490 was previously found to be well tolerated when administered to humans at 15 mg/kg i.v. for 3 consecutive days. Administration of the same dose for 5 consecutive days has now been evaluated in a randomized, double-blind, placebo-controlled study in eight healthy volunteers. The 5-day regimen of ACHN-490 was well tolerated, with mild to moderate adverse events and no evidence of nephrotoxicity or ototoxicity and no QT interval changes. Pharmacokinetics (e.g., high peak and low trough concentrations and a half-life of approximately 3 h) supported a once-daily, high-dose regimen (78). The agent is currently also being investigated in a randomized, double-blind, comparator-controlled phase II trial for the treatment of complicated urinary tract infections and acute pyelonephritis (79).



ACHN-490

The anti-acne nanoemulsion **NB-003** (NanoBio, University of Michigan) was well tolerated in healthy subjects. NB-003 (0.25%) was administered to 25 healthy adults with high levels of *Propionibacterium acnes* on their foreheads and 10 received benzoyl peroxide 2.5% in a randomized study, with treatment applied to the forehead twice daily for 4 weeks. No adverse events occurred and forehead *P. acnes* cultures showed a reduction of 0.46 log_{10} after 1 week and a reduction of 0.66 log_{10} at 4 weeks of NB-003 treatment. Another study of the antiacne activity of NB-003 is under way (80).

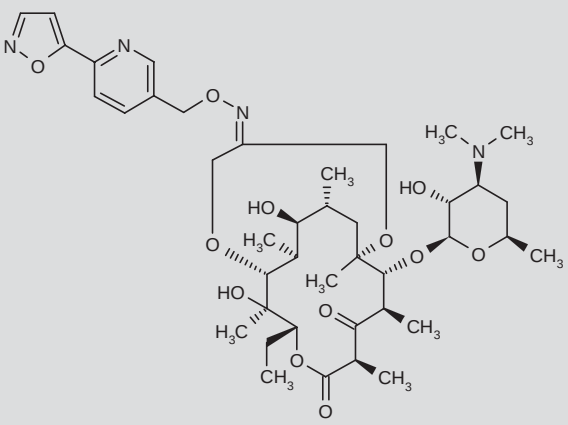
LT-00786 (BioMarin Pharmaceutical), the lead compound from a novel series of vancomycin carbamate derivatives, that demonstrat-



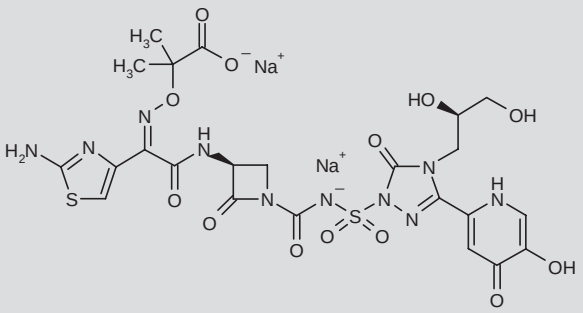
LT-00786

ed potent antibacterial activity against Gram-positive pathogens in vitro and in vivo, supporting further evaluation of the agent for the treatment of bacterial infections. In susceptibility testing in vitro, LT-00786 demonstrated antibacterial activity against multiple drug-resistant bacterial strains including MRSA, vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant enterococci (VRE). The compound inhibited *S. aureus* 757 (MRSA), *S. aureus* 2012 (VISA), *Staphylococcus epidermidis* 831 (MRSE), *Enterococcus faecalis* 848 (VRE, Van A) and *Enterococcus faecium* 752 (VRE, Van A) with MIC values of ≤ 0.015, 0.5, 0.03, 4 and 1 μg/mL, respectively, exhibiting more potent activity than vancomycin (respective MIC values of 1, 8, 2, > 64 and > 64 μg/mL, respectively). Pharmacokinetic profiling of the agent in CD-1 mice revealed very high exposure ($AUC_{[0\text{-inf}]}$ = 134,000 h*ng/mL; > 26-fold higher than vancomycin) and a $t_{1/2}$ of 4.29 h following i.v. administration at 5 mg/kg. In a neutropenic mouse model of lung infection with *S. aureus*, LT-00786 (25 mg/kg i.v.) was more effective than vancomycin or telavancin at reducing bacterial infection at 48 h (81). LT-00786 has been described in the patent literature (WO 2010065174).

At Enanta Pharmaceuticals, refinement of next-generation bicyclic macrolide antibiotics, bicyclolides, led to a novel series of 9-hydroxy-6,11-bicyclolides, that have been evaluated for their antibacterial potency. **EP-017796** was selected as a representative compound and evaluated for its activity against a number of drug-resistant bacteria known to cause infections of the respiratory tract. EP-017796 was associated with MIC values of ≤ 0.06 μg/mL against *S. aureus* with inducible erythromycin resistance, 4 μg/mL against constitutively erythromycin- and methicillin-resistant ermC-positive *S. aureus*, 0.5 μg/mL against erythromycin-resistant erm-positive *S. pneumoniae*, ≤ 0.06 μg/mL against erythromycin-resistant erm-positive *S. pyogenes* and 1 μg/mL against ampicillin-resistant *H. influenzae*. In a mouse protection test dosed 1 and 5 h post-infection, EP-017796 displayed ED_{50} values at 24 h of 12.3 mg/kg against *S. aureus* Smith, 25.1 mg/kg against macrolide-resistant mefA-positive *S. pneumoniae* and 54.4 mg/kg against erm-positive *S. pyogenes* 2912; these ED_{50} values were lower than those seen with telithromycin (82). The bicyclotide has been described in the patent literature (WO 2009137737).



EP-017796



MC-1

To overcome resistance among Gram-negative pathogens, Pfizer has developed novel monocarbam analogues conjugated to a siderophore moiety. One such compound, **MC-1**, has been evaluated in vitro and in vivo and has been described in the patent literature (WO 2010070523). The MIC_{90} of MC-1 against *P. aeruginosa* (n = 138) was 0.5 μg/mL and the agent displayed excellent antipseudomonal activity in in vivo models of systemic and tissue infections. In addition, its aqueous stability was shown to be similar or superior to that of meropenem, with an optimal pH of 6 (83).

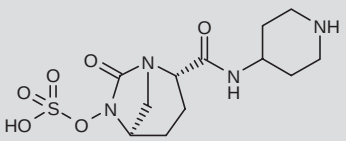
Unlike comparator β-lactams, MC-1 was not a substrate for SHV-, TEM-, KPC- or OXA-type β-lactamases when susceptibility of the agent to enzymatic inactivation was evaluated using an isogenic β-lactamase library constructed in *E. coli*. The mechanism of entry used by MC-1 to penetrate cells was elucidated in *P. aeruginosa*, with a mutation in a single siderophore receptor associated with an eight-fold increase in MIC. This did not, however, result in an increased 50% protective dose (PD_{50}) in a murine model of infection (84).

The MIC_{90} values of MC-1 against the Gram-negative bacteria *Citrobacter koseri*, *Enterobacter aerogenes*, *E. coli*, *K. pneumoniae*, *Serratia marcescens* and *Stenotrophomonas maltophilia* were 0.25, 2, 8, 0.5, 2 and 2 μg/mL, respectively. Activity against multidrug-resistant pathogens was observed and the compound was associated with ED_{50} values of 1.8 and 0.69 mg/kg s.c., respectively, in murine models of *K. pneumoniae* and *P. aeruginosa* acute systemic infection, and 35.7 mg/kg s.c. in a *P. aeruginosa* pulmonary infection model (85).

MC-1 demonstrated high in vitro potency against 416 Gram-negative strains: 97.1% were inhibited at an MIC ≤ 4 μg/mL. A total of 12 *E. coli* strains harboring *ctx-m* genes were inhibited at an MIC ≤ 8 μg/mL. Greater activity was seen with MC-1 than with comparator agents against *P. aeruginosa* and *S. maltophilia* (86).

The crystal structures of MC-1 and other antibiotics in complex with penicillin-binding protein PBP-3 were determined and computational and biophysical analyses were performed. These studies revealed a characteristic of the binding interaction with PBP-3 that distinguishes MC-1 from other known β-lactams, including the presence of several loop regions near the active site (87).

The activity of MC-1 against *P. aeruginosa* UC12120 was also evaluated in vitro and in a neutropenic mouse thigh infection model and a study with pharmacokinetic/pharmacodynamic modeling. Rapid



MK-7655

killing and equivalent potency were observed in vitro and in vivo. Adaptation was minimal in vitro and in vivo. The dose for bacteriostasis versus *P. aeruginosa* in the clinic was predicted to be 275-600 mg i.v. given t.i.d. as a half-hour infusion (88).

The identification of **MK-7655** (Merck & Co.), a novel inhibitor of β-lactamase that has shown promise for the treatment of infections due to Gram-negative bacteria, was described at the meeting. The agent was found to restore the ability of imipenem to eradicate clinical isolates of *P. aeruginosa* and *K. pneumoniae* carrying class A or class C β-lactamases. At concentrations ≥ 8 mg/L, MK-7655 reduced the MIC_{50}/MIC_{90} of imipenem against 10 *K. pneumoniae* isolates expressing plasmid-borne class C β-lactamases to ≤ 2 mg/L (89).

The combination of MK-7655 and the carbapenem imipenem was found to be synergistically bactericidal against the *K. pneumoniae* 6339 strain and the *P. aeruginosa* strains 24226 and 24227 (respective interaction indices of 0.5, 0.6 and 0.7) (90).

The lowest concentrations of MK-7655 that were able to induce a significant reduction in the MIC of imipenem against a variety of β-lactamase-producing strains of *P. aeruginosa* (n = 9) and *K. pneumoniae* (n = 6) were estimated to be 0.5 and 0.13 mg/L, respectively (91).

The pharmacokinetics of the combination of MK-7655 and imipenem at doses of 4-128 mg/kg i.p. were evaluated in vivo in neutropenic mice infected in both thighs with β-lactamase-producing strains of *P. aeruginosa*, *K. pneumoniae* or *Citrobacter freundii*. Linear pharmacokinetics were observed for both imipenem and MK-7655 in the dose range under evaluation, with comparable values for volume of distribution (0.434 and 0.544 L/kg, respectively) and terminal half-life (0.24 and 0.25 h, respectively) (92).

MK-7655 was also evaluated in combination with a subeffective dose of imipenem (5 mg/kg) in mouse models of disseminated *P. aeruginosa* and *K. pneumoniae* infections and in neutropenic mice with pulmonary *P. aeruginosa* infections. At doses of 10, 20 and 40 mg/kg, MK-7655 resulted in respective log CFU reductions of 1.72, 3.13 and 3.73 in mice with systemic *P. aeruginosa* infection. In animals with systemic *K. pneumoniae* infections, MK-7655 administered at 20, 40 and 80 mg/kg resulted in log reductions in CFU of 2.29, 3.06 and 2.36, respectively. The agent exhibited a static effect at a dose of 20 mg/kg in combination with imipenem in mice with established pulmonary *P. aeruginosa* infection (93).

Human pharmacokinetic and dose projection studies of MK-7655 revealed minimal metabolism of the compound in incubations of liver microsomes/hepatocytes. The projected clearance value for the agent in human plasma was estimated at 1-3 mL/min/kg, which corresponded to a clinical i.v. dose of 230-860 mg/day (94).

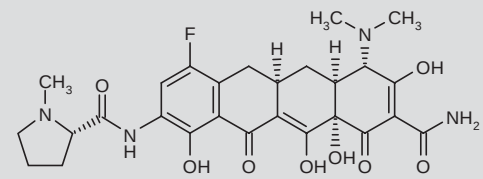
In a randomized, double-blind, placebo-controlled, single-ascending-dose trial, a total of 16 healthy subjects received treatment with MK-7655 (single doses of 25-1150 mg), a combination of imipenem and cilastatin (500 mg Primaxin® i.v.), Primaxin® i.v. plus MK-7655 at doses of 50 and 500 mg or placebo. Dose-proportional increases in the levels of MK-7655 were observed followed by an exponential decline. The agent's half-life was established at 1.3-1.8 h. The coadministration of Primaxin® i.v. and MK-7655 had no effect on the concentration of MK-7655, imipenem or cilastatin. Treatment with MK-7655 was described as well tolerated. The findings support additional evaluation of the combination regimen of Primaxin® i.v. and MK-7655 (95). MK-7655 has been described in the patent literature (WO 2009091856).

Data from several studies on the novel, broad-spectrum fluorocycline antibiotics **TP-271** and **TP-434** (Tetraphase Pharmaceuticals) were presented. The fully synthetic fluorocycline analogues TP-271 and TP-434 were generated by the introduction of a fluorine atom at position C7 coupled with the presence of a pyrrolidino moiety at position C9 of tetracycline (96).

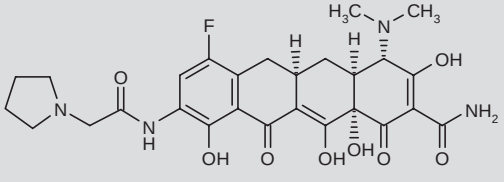
TP-271 demonstrated potent activity against community-acquired respiratory pathogens, such as MRSA, *S. pneumoniae, S. pyogenes, M. catarrhalis* and *H. influenzae* (respective MIC_{50} = 0.031, ≤ 0.016, ≤ 0.016 and 0.25 μg/mL) and against biothreat pathogens, including *Yersinia pestis*, *Bacillus anthracis*, *Francisella tularensis* and *Burkholderia mallei* (respective MIC_{50} = 0.12, ≤ 0.008, 0.25 and 0.06 μg/mL) (97).

TP-434 was identified using a total synthesis approach that involved the systematic modification of the D-ring of tetracycline. The agent exhibited equipotent inhibitory activity against protein synthesis in the presence or absence of ribosomal protection conferred by addition of the tetracycline resistance protein tetM (98).

When evaluated against a panel of clinical isolates, TP-434 displayed MIC values of ≤ 0.5 μg/mL against all Gram-negative bacte-



TP-271



TP-434

rial strains. It was found to be twofold more active than tigecycline against *A. baumannii* isolates that exhibited 44% resistance to carbapenems, 53% to tetracycline and 64% to fluoroquinolones (99).

Both TP-434 and TP-271 demonstrated markedly higher activity than tetracycline against *Legionella pneumophila* serogroups 1-6 (respective MIC_{50} values of 1, 0.25 and 4 mg/mL against all serogroups) (100).

The agents were shown to bind to empty ribosomes with higher potency than tetracycline (approximately 14- and 17-fold higher, respectively, for TP-434 and TP-271) and inhibited in vitro transcription/translation with potencies that exceeded those of tetracycline by approximately 4.3- and 7-fold, respectively (101).

Additional preclinical evaluation of TP-434 revealed high metabolic stability in cells derived from rats, dogs, monkeys and humans, with 103.2%, 95%, 94% and 85.3%, respectively, of the agent remaining after 4 h of incubation. No inhibition of cytochrome P450 enzymes was observed, suggesting a low possibility for drug–drug interactions (102).

Pharmacokinetic analysis of TP-434 in chimpanzees following i.v. administration at 1 mg/kg revealed peak plasma concentrations of 0.5-1.3 µg/mL, which declined in a multiphasic manner, and a terminal elimination half-life of 10.2 h. The oral bioavailability (after a dose of 10 mg/kg p.o.) was estimated at 29.2% (103).

Treatment with TP-434 conferred significant protection against septicemia in mice infected with *S. aureus*, including tetracycline-resistant *S. aureus* and MRSA, and *S. pyogenes* ($PD_{50} \leq 1$ mg/kg). The agent also reduced the burden of MRSA and *S. pneumoniae* in the lungs of infected mice at doses of 10 and 30 mg/kg i.v., respectively, with efficacy equivalent to or higher than that of linezolid at 30 mg/kg p.o (104).

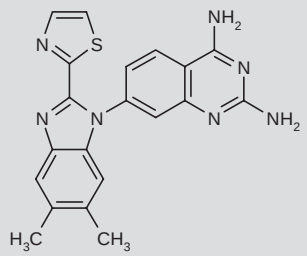
Neutropenic CD-1 mice injected in the right thigh with a tetracycline-resistant strain of MRSA (USA300) received TP-434 at doses of 1-60 mg/kg s.c. in order to establish the pharmacodynamic/pharmacokinetic parameter that could best predict the efficacy of the agent against bacterial infections. The 24-h total AUC/MIC ratios required to achieve a static effect and a 1-log decrease in CFU were estimated at 38.4 and 46.9, respectively. The C_{max}/MIC ratio at stasis was calculated at 1.64. The activity of TP-434 in this model correlated best to the AUC/MIC ratio, which predicted efficacy of the agent in humans at a daily dose of 1.5 mg/kg i.v. (105).

The safety, tolerability, pharmacokinetics and urinary excretion of single ascending doses of TP-434 (0.1, 0.25, 0.5, 1, 1.5, 2 and 3 mg/kg) were evaluated in a phase I trial in 56 healthy individuals. Pharmacokinetic profiling indicated dose-proportional and linear exposure (AUC, C_{max}) in the plasma. The agent's half-life at all doses was estimated to be in the range of 12-24 h. Safety analysis revealed gastrointestinal side effects at doses of ≥ 2 mg/kg, with no clinically significant changes in ECG or laboratory parameters and no serious adverse events being reported in this study (106).

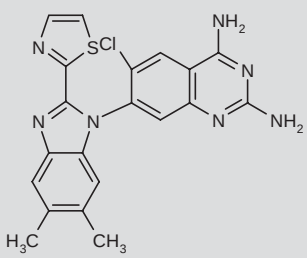
In a multiple-ascending-dose trial, TP-434 was administered at 0.5 and 1.5 mg/kg once daily over 30 min, 1.5 mg/kg once daily over 1 h and 1 mg/kg b.i.d. over 1 h for a period of 10 days to healthy volunteers (n = 6 and 2, respectively, receiving active treatment and placebo in each cohort). Dose-proportional pharmacokinetics that could be described by a four-compartment model were observed. The data confirmed that the elimination of the compound was achieved mainly via nonrenal pathways and suggested that sufficient exposure of the agent to treat infections caused by multidrug-resistant Gram-negative aerobic and facultative bacilli, as well as Gram-positive pathogens, could be attained at doses of 1.5 mg/kg once daily or 1 mg/kg b.i.d (107). TP-271 and TP-434 have been described in the patent literature (WO 2010017470).

Using a structure-based design, researchers at Trius Therapeutics identified novel antibacterial inhibitors of dihydrofolate reductase (DHFR) that are based on a 7-aryl-2,4-diaminoquinazoline scaffold. Substitutions on the aryl group of 7-aryl-2,4-diaminoquinazolines increased the potency for DHFR, especially with the 7-(benzimidazol-1-yl)-2,4-diaminoquinazolines, represented by **Rx-101005** (*S. aureus* MIC = 0.015 µg/mL; *S. aureus* DHFR K_i = 0.002 nM) (108).

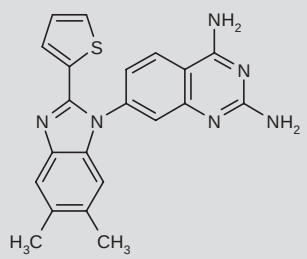
In addition to Rx-101005, the 7-(benzimidazol-1-yl)-2,4-diaminoquinazolines bearing heterocycles at the 2 position of the benzimid-



Rx-101005



Rx-101079



Rx-101127

azole ring also included **Rx-101079** (*S. aureus* MIC = 0.125 μg/mL; *S. aureus* DHFR K_i = 0.011 nM) and **Rx-101127** (*S. aureus* MIC = 0.015 μg/mL; *S. aureus* DHFR K_i = 0.005 nM). Compounds in this series were active against trimethoprim-susceptible and -resistant *S. aureus* and had greater selectivity ratios than trimethoprim versus the human DHFR enzyme (109).

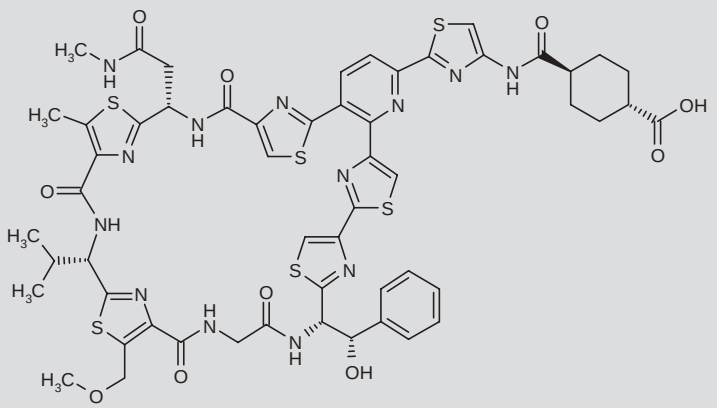
In addition to showing activity against *S. aureus* strains, 7-(benzimidazol-1-yl)-2,4-diaminoquinazolines including Rx-101005, Rx-101079 and Rx-101127 were active against a panel of *S. pneumoniae* strains, including the multidrug-resistant strain ATCC 700904. Rx-101005 and Rx-101079 displayed synergy with sulfamethoxazole against *S. aureus* ATCC 13709 (110).

Rx-101005 displayed potency against wild-type *S. aureus* and against the trimethoprim-resistant mutant strain F99Y (MIC = 0.25 μg/mL). The compound was synergistic with sulfamethoxazole at lower concentrations than trimethoprim/sulfamethoxazole combinations. In time-kill studies, Rx-101005 at 2, 4 and 12 times the MIC was associated with a 3-log drop in CFU by 6 h, with the 12-fold MIC concentration maintaining the effect for 24 h. The compound was highly effective in vivo against wild-type *S. aureus* infection (ED_{50} = 1.8 mg/kg i.v.) and was well tolerated at the doses tested (1.6-50 mg/kg i.v.); trimethoprim was ineffective in this model (111).

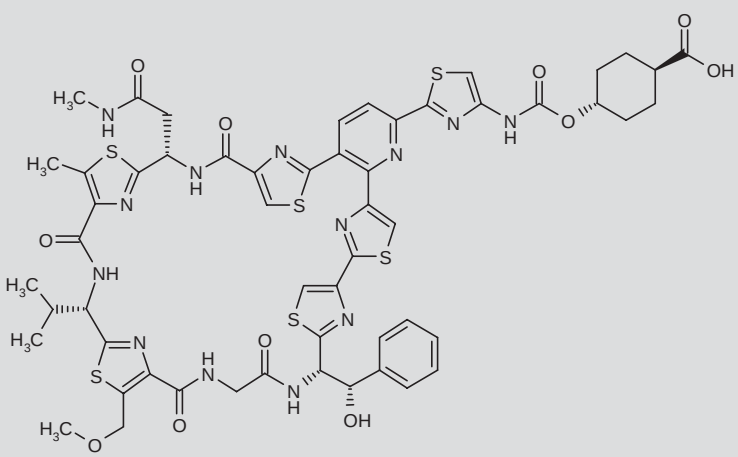
Investigators at Novartis have designed and prepared semisynthetic analogues of the thiopeptide-based natural product GE-2270 in an effort to identify agents with activity against Gram-positive organisms. Medicinal chemistry efforts guided by cocrystal studies led to the identification of the development candidates **LDI-028** and **LDK-733** (112).

In vitro susceptibility studies using *S. aureus* and *Enterococcus* spp. and phenotypic and genotypic characterization of mutants indicated that the GE-2270 analogues inhibited bacterial elongation factor Tu (EF-Tu). Selected mutants had changes in the *tuf* gene and displayed reduced susceptibility to GE-2270 and derivatives but not to antibiotics with a different mechanism of action (113).

LDI-028 and LDK-733 and other GE-2270 analogues demonstrated in vitro activity against Gram-positive bacteria. Postantibiotic effect



LDI-028



LDK-733

(PAE) experiments revealed that six bacterial pathogens recovered from exposure to LDI-028 in a similar fashion as control organisms that had not been exposed to the agent. LDK-733, however, displayed a postantibiotic effect of ≥ 2.5 h against *E. faecalis* and of approximately 2 h against *S. aureus* and *E. faecium* after 1-h exposure at 2 x MIC. LDI-028 and LDK-733 were bactericidal against *S. aureus* and bacteriostatic against *E. faecalis* and *E. faecium*. Modest cytotoxicity was seen with the compounds in three human cell lines. LDI-028 and LDK-733 did not show synergy with or antagonism of vancomycin, daptomycin or gentamicin in checkerboard tests against three Gram-positive pathogens, while LDK-733 appeared to interact positively with ampicillin against *E. faecalis* (114).

When pharmacokinetics and pharmacodynamics were assessed with LDI-028 in the neutropenic mouse thigh infection model using *S. aureus* ATCC 29213, AUC/MIC was the parameter that correlated best with the drug's efficacy. Peak/MIC was also strongly correlated with activity, while little correlation was seen with time above MIC (115).

LDI-028 and LDK-733 protected mice from lethal systemic *E. faecalis* infection with respective ED_{50} values of 0.56 and 0.23 mg/kg i.v., both displaying greater potency than daptomycin. The agents were significantly less potent than daptomycin against systemic *S. aureus* infections, with respective ED_{50} values of 5.2 and 4.3 mg/kg i.v. (116).

Preclinical and phase I data were presented on Algipharma's **OligoG**, an oligosaccharide derived from alginate polysaccharide that is under development at AlgiPharma as a potential treatment for cystic fibrosis and also as an antimicrobial. Here we summarize data from several preclinical studies and one clinical trial of the product.

When tested in vitro against Gram-positive isolates, OligoG showed little or no synergistic activity in combination with tobramycin, amikacin, imipenem, ciprofloxacin, colistin or oxytetracycline. It did, however, display synergy with macrolides and β-lactams against most bacteria, including MRSA (117).

MIC values for azithromycin, imipenem, ceftazidime, aztreonam and erythromycin against multidrug-resistant *Burkholderia cepacia* and *Burkholderia multivorans* strains were reduced when 10% OligoG was coadministered. Synergy against *P. aeruginosa* was observed when OligoG was combined with azithromycin, erythromycin, clarithromycin and ceftazidime. The agent also disrupted *B. cepacia* and *P. aeruginosa* biofilms (118).

Against resistant *A. baumannii*, OligoG potentiated the antimicrobial effects of aztreonam, ciprofloxacin, meropenem, ceftazidime and azithromycin, reducing the compounds' MIC values up to fivefold. OligoG also severely disrupted *A. baumannii* biofilms (119).

When male Sprague-Dawley rats were given single oral doses of [^{3}H]-OligoG, absorption was rapid, with the highest mean plasma concentration of nonvolatile radioactivity observed 2 h after dosing. Excretion was also rapid and occurred primarily via feces (88.1%). After administration of the product as a single i.v. dose, the highest mean concentration of nonvolatile radioactivity was seen 5 min after dosing and the major route of elimination was via the urine (79.5%) (120).

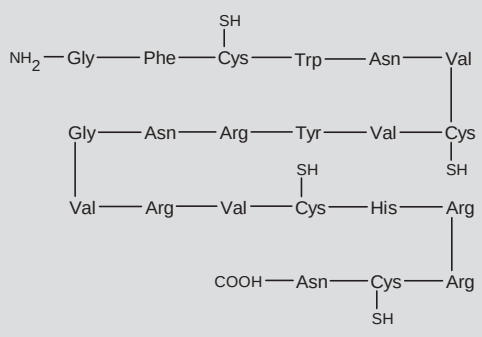
The effects of OligoG aerosol on respiratory parameters were investigated in male rats given a single 4-h inhalation, with no effects on respiratory rate, tidal volume or respiratory minute volume seen at OligoG doses of 163, 176 or 330 mg/kg (121).

Rats exposed to single inhalations of 6% OligoG lasting 60, 120 or 240 min displayed no adverse reactions or abnormal clinical signs. No treatment-related changes in body weight, hematology, clinical chemistry, urinary parameters or respiratory parameters were observed. Increases in lung weight were noted in male animals (122).

The toxicology of the agent was assessed in rats receiving once-daily inhalation of 6% OligoG for 7, 14 or 28 days. No adverse reactions occurred, nor did treatment-related changes in hematology or clinical chemistry parameters, urinalysis or respiratory parameters. Dose-dependent increases in lung weight were observed in male but not female animals. Necropsies revealed bronchial lymph node enlargement in eight animals. Histopathological investigation revealed alveolar macrophage accumulation, a normal adaptive response to inhaled material in the lungs (123).

A placebo-controlled phase I study evaluated the safety and tolerability of aerosolized OligoG in healthy volunteers. A total of 28 healthy men received a single dose of aerosolized 6% OligoG (90 mg in 1.5 mL) or 3 days of OligoG therapy at dosages of 90 mg/day in 1.5 mL once daily, 270 mg/day in 4.5 mL once daily or 540 mg/day in 4.5 mL b.i.d. or matched placebo. No adverse events were seen with the single 90-mg dose or doses of 90 mg/day. In subjects receiving multiple doses at 270 mg/day, two OligoG-treated individuals experienced adverse events (mild headache). In the highest multiple-dose group, three OligoG-treated subjects had adverse events of mild dry cough, but adverse events did not differ from those observed in participants receiving placebo. Overall, no serious adverse events, discontinuations or significant changes in laboratory values or vital signs occurred (124).

Several studies have evaluated the antimicrobial potential of **NZ-17074** (Novozymes), a variant of the arenicin-3 polypeptide isolated from the marine worm *Arenicola marina*. To identify arenicin-3 variants with reduced protein binding, error-prone PCR mutagenesis was performed on the arenicin-3 sequence scaffold to generate variants, which were screened against *E. coli* and *Pseudomonas* using



NZ-17074

plate assays containing 2.5% blood. One of the identified variants, NZ-17074, was found to be as potent in MIC testing against *E. coli* and *Pseudomonas* spp. as arenicin-3 but had lower protein binding capacity in 90% serum (79% vs. 99%) (125).

NZ-17074 was active against multidrug-resistant *Enterobacteriaceae* isolates and was associated with MIC values of 0.5-16 µg/mL against *P. aeruginosa* and nonfermenters, with bactericidal activity observed. In time-kill experiments, it had a concentration-dependent effect and reduced the amount of viable bacteria by 3 log (99.9%) within 2 h (126).

When NZ-17074 was administered to healthy NMRI mice at 5 mg/kg s.c., the agent exhibited concentration-dependent protein binding (approximately 84%), a half-life of 60 min and 62% bioavailability. Pharmacokinetics of the compound were similar between healthy mice and neutropenic mice injected i.p. with a multidrug-resistant *E. coli* strain. Within 4 h, NZ-17074 significantly decreased the bacterial concentration by 3 log in the animals compared with vehicle (127).

Efficacy in a murine peritonitis/sepsis model was seen when neutropenic mice inoculated with a multidrug-resistant *E. coli* strain received single doses of NZ-17074 i.v., with the ED_{50} values calculated at 3.1 mg/kg in peritoneal fluid and 3.2 mg/kg in blood. The dose associated with 1-log killing was 1.1 mg/kg in the peritoneum and 0.25 mg/kg in blood. A single dose of 7.5 mg/kg significantly reduced the amount of *E. coli* in peritoneal fluid (3.88 $\log_{10}$ CFU/mL) and in blood (3.7 $\log_{10}$ CFU/mL) at 5 h. These effects were superior to those of meropenem 40 mg (128).

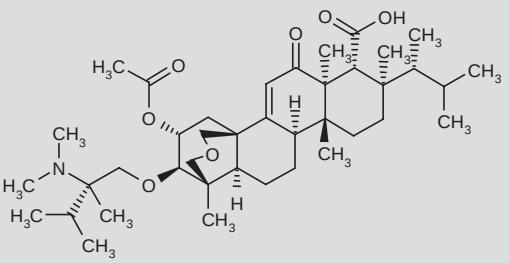
A neutropenic thigh infection study in mice inoculated with a multidrug-resistant *E. coli* strain found the ED_{50} of NZ-17074 to be 5.9 mg/kg, the 1-log killing dose to be 6.1 mg/kg and the E_{max} to be 2.4 $\log_{10}$ CFU/mL. In a murine model of urinary tract infection with a multidrug-resistant *E. coli* strain, two daily doses of 10 mg/kg significantly reduced bacterial loads in the urine, bladder and kidneys. The activity in kidneys in this model was significantly better with NZ-17074 than with meropenem 40 mg (129). NZ-17074 has been described in the patent literature (WO 2007023163).

Preliminary phase I data on the anti-PNAG fully human IgG_1 monoclonal antibody (MAb) **F-598** were disclosed at ICAAC. F-598 targets the broadly expressed bacterial surface polysaccharide poly-*N*-acetyl glucosamine (PNAG) and has been described as an attractive candidate for the prevention of infections with *S. aureus* and other PNAG-producing pathogens. Researchers presented data from the IND-enabling toxicity and efficacy studies in animals, as well as initial data from the first phase I trial. In tissue reactivity studies, F-598 did not bind to a panel of 33 human tissues and organs. Toxicological assessment in CD-1 mice revealed no adverse effects following administration of the agent as a single i.v. dose (100 mg/kg). No detectable systemic toxicity was reported in mice injected with F-598 in conjunction with a sublethal dose of *S. aureus*. Therapeutic administration of F-598 given either systemically (i.p.) or topically (intraocularly) correlated with a significant decrease in corneal pathology and a reduction in *S. aureus* burden at 48 h postinfection in mice with experimental keratitis. In a murine model of skin abscess, prophylactic i.p. injection with F-598 resulted in a significant reduction in the yield of *S. aureus* recovered from abscesses at 72 h post-infection. Based on encouraging preclinical data, a phase I trial of F-598 in healthy volunteers is currently under way. A single 2-h i.v. infusion of the antibody has been administered at doses of 1, 5, 10, 15 and 20 mg/kg to healthy individuals (n = 4/dose level). Preliminary results from the 1 mg/kg cohort revealed a long elimination half-life (approximately 27 days), low systemic clearance (0.0716 mL/h/kg) and low volume of distribution (62 mL/kg) (130). Originally developed by Brigham & Women's Hospital, F-598 was licensed to Alopexx Pharmaceuticals, which entered into a collaboration agreement for the MAb with sanofi-aventis in 2009.

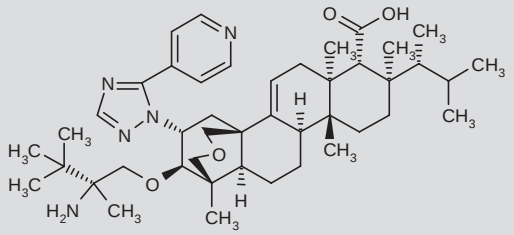
Researchers from Phico Therapeutics presented data from a randomized, double-blind, placebo-controlled phase I study of the antibacterial gene therapy **PT1.2**. PT1.2 is an *S. aureus*-specific bacteriophage phi 11 modified so that the gene encoding holin has been replaced by the *Bacillus megaterium sasP-C* gene, leading to expression of small, acid-soluble spore protein C (SASP). Healthy male subjects received placebo or PT1.2 in a single-dose phase evaluating doses of 1×10^7 and 1×10^8 PFU administered in each nostril and in a multiple-dose phase in which a 1×10^8 PFU dose was administered in each nostril twice daily for 5 days and once daily on day 6. The single-dose phase included 8 *S. aureus* carriers and 8 non-*S. aureus* carriers and all 14 subjects in the multiple-dose phase were *S. aureus* carriers. No serious or severe adverse events were reported and none led to treatment discontinuation. The incidence of treatment-related adverse events was not dose-related and all were mild and transient. Nasal tolerability scores indicating hyperemia and inflammation also did not differ between dose groups, and the majority of subjects had normal scores. *S. aureus* status did not appear to alter the frequency of adverse events in the single-dose phase. PT1.2 was not associated with systemic exposure or changes in clinical laboratory parameters, vital signs or electrocardiograms. Additionally, the agent was found to be able to boost preexisting antibody responses to PT1.2 or the parental bacteriophage phi 11 (131).

ANTIFUNGALS

Encouraging data were disclosed by Merck & Co. and Scynexis on several new enfumafungin derivatives that exhibit potent antifungal activity by inhibiting the enzyme 1,3-β-glucan synthase. The addition of a 12-oxo group to 3-aminoether-25-deoxy derivatives of the triterpene enfumafungin resulted in the generation of compounds with robust antifungal activity. A representative compound, **1**, exhibited high potency against *Candida albicans* infections in DBA/2N mice



1



MK-3118

(ED_{99} = 4) and CD rats (ED_{99} < 2.5) following oral administration. In DBA/2N mice infected with *Aspergillus fumigatus*, oral dosing of **1** at 50 mg/kg b.i.d for 7 days markedly increased the survival of the animals (38%) versus vehicle. The compound demonstrated good oral bioavailability in mice, rats, dogs and monkeys (22-55%) (132).

The introduction of a 2-heterocycle and a 3-aminoalkyl ether group gave rise to agents with improved in vivo inhibitory activity against *C. albicans*. These agents exhibited low MIC values against *C. albicans* and low minimum effective concentration (MEC) values against *A. fumigatus*. A selected compound from this series, **MK-3118** significantly reduced the *C. albicans* burden in the kidneys of mice with disseminated candidiasis in the target organ kidney assay when administered at > 3.1 mg/kg i.v. or > 6.2 mg/kg b.i.d. p.o. for 2 days, compared with vehicle (133).

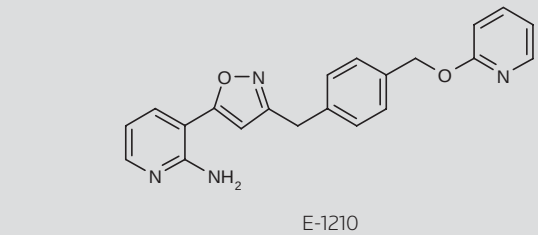
When administered to DBA/2N mice at 25 mg/kg p.o., MK-3118 reduced the burden of infection with *Candida tropicalis* in the kidneys by 2.6-3.8 log CFU/g compared with vehicle control (134).

Treatment with MK-3118 (1.56-12.5 mg/kg b.i.d. i.p. for 7 days) prolonged survival in both DBA/2N and neutropenic CD-1 mice infected with the *A. fumigatus* strain MF5668. In neutropenic mice, the prolongation of survival was associated with a dose-dependent decrease in the burden of *A. fumigatus* in the kidneys relative to values in vehicle-treated animals (4.7-log reduction in burden at a dose of 12.5 mg/kg and no detectable burden on day 14 of treatment at this dose level) (135).

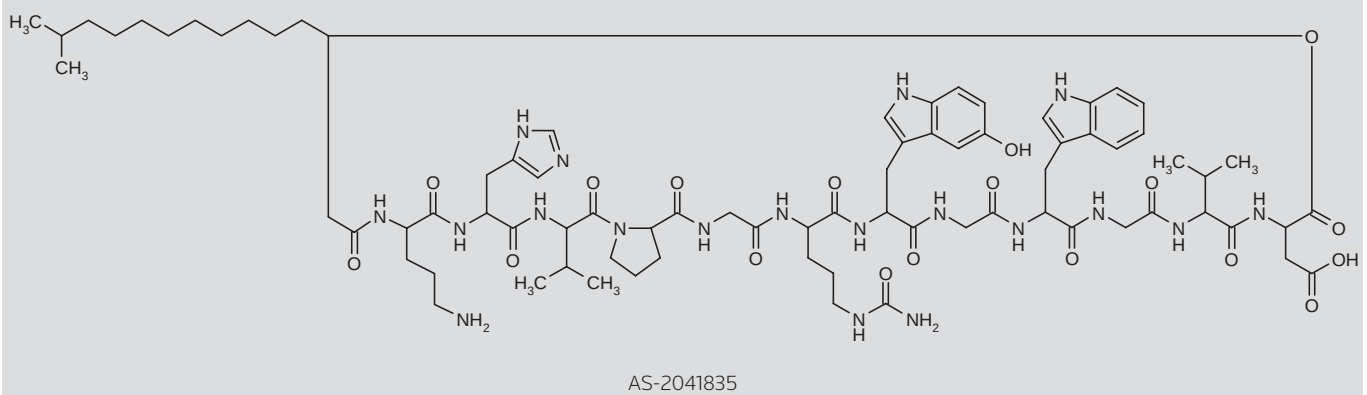
In vitro MK-3118 displayed broad-spectrum activity against 160 clinical isolates of 7 *Candida* species (MIC_{90} ≤ 1 μg/mL) and 40 clinical isolates of 4 *Aspergillus* species (MEC_{90} ≤ 0.015 μg/mL). A low frequency of spontaneous mutations that confer decreased susceptibility to MK-3118 was reported in *C. albicans* (< 4.6 x 10^{-9} mutations/cell/generation) (136).

AS-2041835 (Astellas Pharma), a novel natural depsipeptide isolated from the bacterium *Paenibacillus* sp. strain 530603, was reported to exhibit potent antifungal activity in combination with micafungin sodium against *A. fumigatus* in a recent preclinical study. In vitro AS-2041835 inhibited the growth of *A. fumigatus* FP1305 with MEC and MIC values of 3.13 and > 50 μg/mL, respectively, and displayed a synergistic effect with micafungin (MEC = 0.4 μg/mL; MIC = 3.1 μg/mL). In vivo, coadministration of AS-2041835 (32 mg/kg) and micafungin (0.1 mg/kg) in *A. fumigatus*-infected mice significantly prolonged survival versus micafungin alone (P = 0.085). The results support additional evaluation of the combination therapy for the treatment of *A. fumigatus* infections (137).

Eisai's novel broad-spectrum antifungal agent **E-1210** acts by inhibiting the biosynthesis of fungal glycosylphosphatidylinositol (GPI). Its activity in vitro and in vivo has been explored in multiple investigations which were detailed at the congress. E-1210 was found to inhibit inositol acylation of fungus-specific GPI, a process catalyzed by GPI-anchored wall transfer protein 1 (Gwt1p), resulting in inhibition of GPI-anchored protein maturation. These effects led to growth defects and reduced expression of some virulence factors of *C. albicans* (138).



E-1210



AS-2041835

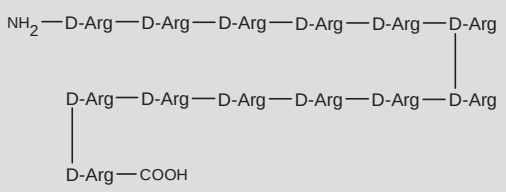
E-1210 was evaluated against 247 clinical isolates of fungal pathogens, demonstrating high activity against *Candida* spp. and *Aspergillus* spp., with strong activity against fluconazole-resistant *Candida* strains. The greatest activity was seen against *Pseudallescheria boydii*, *Scedosporium prolificans* and *Paecilomyces lilacinus,* and the agent was active against *Fusarium solani* and some black molds (139).

The total fungal burden in murine kidney homogenates was reduced by E-1210 in a model of disseminated candidiasis, with efficacy correlating with AUC/MIC and time above MIC more than with C_{max}/MIC. The E-1210-associated reduction in mortality also correlated best with AUC/MIC and time above MIC. In addition, the agent had significant, concentration-dependent post-antifungal effects in vitro and in vivo (140).

Studies in murine models showed that oral E-1210 effectively treated oropharyngeal candidiasis, disseminated candidiasis caused by azole-susceptible and azole-resistant *C. albicans*, disseminated fusariosis caused by *F. solani* and pulmonary aspergillosis caused by *Aspergillus flavus* and *A. fumigatus* (141).

Finally, E-1210 pharmacokinetics were characterized in mice, rats, dogs and monkeys, revealing low to moderate plasma clearance, a moderate volume of distribution and oral bioavailability of 58-73%. Toxicological analyses in rats revealed no hindrances to further development. Morbidity and mortality apparently caused by anorexia and/or gastrointestinal lesions were seen at 1000 mg/kg, and adaptive hepatocellular hypertrophy was observed at doses ≥ 300 mg/kg (142).

NovaBiotics researchers presented data on the in vitro and in vivo antifungal activity of the cationic peptide **NP-339**. Against a panel of more than 200 *Candida* spp. isolates, including those with reduced susceptibility or resistance to azoles, the peptide was candidacidal within 30 min and associated with MIC_{100} values of 1-512 µg/mL (median 2 µg/mL). Activity was also seen against clinically relevant yeasts and molds, including *Aspergillus* spp., *Fusarium* spp. and *Cryptococcus* spp. When the *C. albicans* strain SC5314 was exposed to NP-339 concentrations below the MIC for more than 65 passages, no increase in MIC was seen. Physiological salt concentrations or serum did not significantly alter the compound's activity. In a murine model of acute candidiasis (infection with *C. albicans* strain SC5314), PEGylated NP-339 reduced fungal burden at 5 mg/kg but was tolerated at up to 10 mg/kg. The agent will be formulated for both i.v. and oral delivery and assessed for its potential to be coadministered with other antifungal compounds (143).



NP-339

ANTIMALARIALS

Artemether sublingual spray (Artimist™; Proto Pharma) was safe and well tolerated in children with malaria caused by *Plasmodium falciparum* infection in a recent open-label, randomized, active-controlled phase II study. Children with severe/complicated malaria or uncomplicated malaria with gastrointestinal complications (N = 30) were randomized to receive treatment with artemether sublingual spray (6 doses of 3 mg/kg) or quinine (20 mg/kg i.v. loading dose followed by 10 mg/kg i.v. every 8 h). The trial's primary endpoint was parasitological success, defined as ≥ 90% reduction in parasite count versus baseline levels at 24 h after the initial dose. It was achieved by 93.3% and 66.7% of subjects, respectively, treated with artemether sublingual spray and quinine. No statistically or clinically significant difference was observed between the two treatments at all other outcome measures, including parasite reduction ratio at 12 and 24 h after administration and parasite clearance time (144).

Pharmacokinetic analysis of artemether sublingual spray (3 mg/kg) given to 15 children with malaria at 0, 8, 24, 36 48 and 60 h revealed rapid absorption, resulting in high concentrations of both artemether and dihydroartemisinin in the plasma (C_{max} = 271 and 106.5 ng/mL, respectively) shortly after dosing (within 1.6 and 1.75 h after administration, respectively). Negative parasite counts were recorded in 86.7% of the patients by day 2 following treatment initiation (145).

Clinical data presented on **sevuparin** in healthy adults supported evaluation in a phase II trial in malaria. Researchers at Dilafor disclosed encouraging data on the heparin derivative, and the agent is expected to enter a phase II study conducted in Asia or Africa in adults with malaria (146). The safety, tolerability, pharmacokinetics and pharmacodynamics of sevuparin were evaluated in a double-blind, placebo-controlled, first-in-human trial performed in healthy subjects. The agent was administered i.v. as single doses (10, 30, 90, 180, 360 or 420 mg) or multiple doses (180 or 360 mg; nine doses over a period of 3 days). In the single-dose sevuparin cohort, dose-proportional increases were reported in the C_{max} (mean C_{max} = 2.7-114 µg/mL) and the $AUC_{(0\text{-last}),}$ which was estimated at 7.1-140 h.µg/mL. The mean terminal half-life was 0.66-1 h and independent of the dose. There was no accumulation of sevuparin following administration of multiple doses. The C_{max}, $AUC_{(0\text{-}6\ h)}$ and t_{max} values were similar after single or multiple dosing. In pharmacodynamic analysis, minor dose-dependent increases in the activated partial thromboplastin time were observed, although these did not correlate with relevant changes in prothrombin time, thrombin time or platelet function. Safety assessments revealed no serious adverse events or relevant adverse events following treatment with sevuparin. The findings support additional evaluation of the agent in patients with severe, life-threatening malaria (147).

DISCLOSURES

The authors state no conflicts of interest.

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