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MONOGRAPH

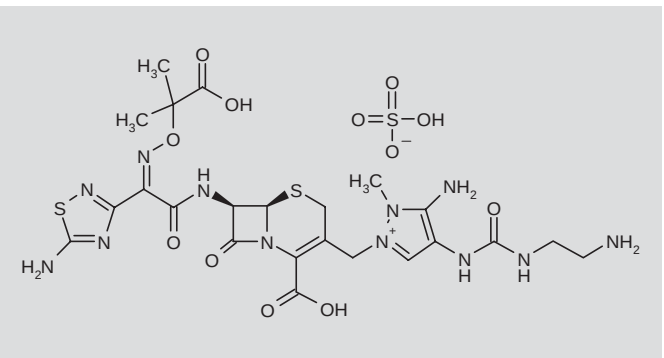
CXA-101

Cephalosporin Antibiotic

FR-264205
CXA-301 (inhalation formulation)

(6*R*,7*R*)-3-[5-Amino-4-[3-(2-aminoethyl)ureido]-1-methyl-1*H*-pyrazol-2-ium-2-ylmethyl]-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(*Z*)-1-carboxy-1-methylethoxyimino]acetamido]-3-cephem-4-carboxylic acid hydrogensulfate

InChI: 1S/C23H30N12O8S2.H2O4S/c1-23(2,20(40)41)43-31-11(15-30-21(26)45-32-15)16(36)29-12-17(37)35-13(19(38)39)9(8-44-18(12)35)6-34-7-10(14(25)33(34)3)28-22(42)27-5-4-24;1-5(2,3)4/h7,12,18,25H,4-6,8,24H2,13H3,(H7,26,27,28,29,30,32,36,38,39,40,41,42);(H2,1,2,3,4)/b31-11-;/t12-,18-;/m1./s1



$C_{23}H_{32}N_{12}O_{12}S_3$
Mol wt: 764.768
CAS: 936111-69-2
EN: 371449

SUMMARY

CXA-101 is a novel broad-spectrum cephalosporin active against highly resistant clinical isolates and laboratory strains of Pseudomonas aeruginosa, including isolates resistant to ceftazidime, multidrug-resistant isolates, AmpC-hyperproducing clones and highly resistant cystic fibrosis isolates. Activity appears not to be affected by efflux mechanisms, porin deficiency or altered penicillin-binding proteins (PBPs). CXA-101 is very stable and not substantially affected by mutation-mediated mechanisms of resistance. It conserves activity against some extended-spectrum β-lactamase (ESBL)-expressing isolates, but not against metallo-β-lactamases. The activity profile for non-pseudomonal isolates is comparable to that of third-generation cephalosporins. CXA-101 is administered i.v. and more than 90% of the unmodified drug is secreted via the kidneys. The plasma half-life is approximately 2 h. No drug accumulation occurred in subjects receiving multiple doses of the drug. Phase I and II safety analysis showed that CXA-101 is well tolerated. A randomized phase II trial in patients affected by complicated urinary tract infections has been recently completed. Current available data on CXA-101 are promising and endorse further clinical development of this agent. The drug is foreseen to be further investigated and developed in combination with the β-lactamase inhibitor tazobactam (CXA-201).

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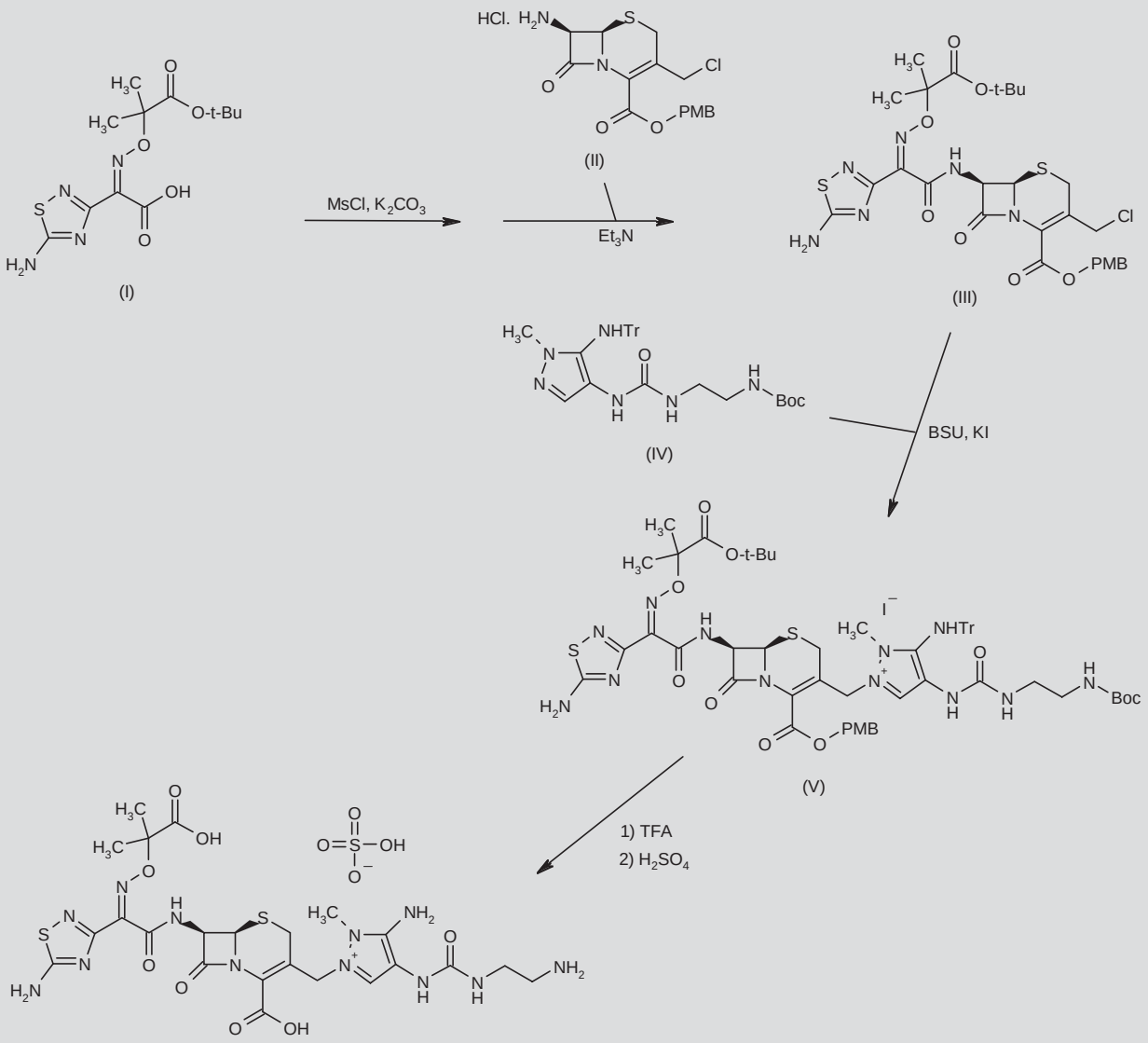
SYNTHESIS*

Activation of the thiadiazolyl-oximinoacetic acid derivative (I) with methanesulfonyl chloride and K_2CO_3 in DMA at 10 °C, followed by coupling with the 7-aminocephem (II) by means of Et_3N in cold EtOAc/H_2O, affords amide (III) (1). Substitution of the allylic chloride of compound (III) with 4-[(*N*-Boc-aminoethyl)carbamoylamino]-1-methyl-5-tritylaminopyrazole (IV) in the presence of 1,3-bis(trimethylsilyl)urea (BSU) and KI in DMF then affords the protected pyrazolium adduct (V), which, after full deprotection with trifluoroacetic acid in anisole/CH_2Cl_2, is isolated as the hydrogensulfate salt by treatment with H_2SO_4 in *i*-PrOH/H_2O (1, 2). Scheme 1.

The pyrazolyl urea intermediate (IV) is prepared as follows. Treatment of 5-amino-1-methylpyrazole (VI) with $NaNO_2$/HCl in water at 5 °C gives the 4-nitrosopyrazole derivative (VII), which is reduced to the diaminopyrazole (VIII) by catalytic hydrogenation over Pd/C in the presence of H_2SO_4. Selective acylation of the 4-amino group of compound (VIII) with phenyl chloroformate in the presence of NaOH in H_2O/dioxane at 10 °C then yields the phenyl carbamate (IX). After protection of the free amine group of carbamate (IX) with chlorotriphenylmethane in the presence of Et_3N in THF, the resulting *N*-trityl derivative (X) is coupled with *N*-Boc-ethylenediamine (XI) in

Scheme 1. Synthesis of CXA-101



the presence of Et_3N in DMF to afford pyrazolyl urea (IV) (1, 2). Scheme 2.

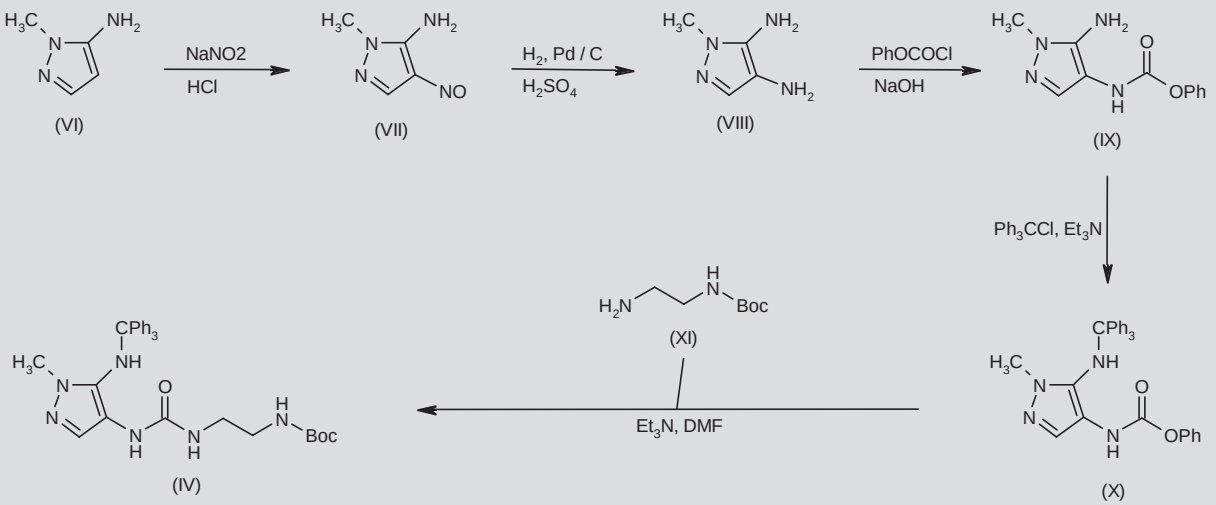
BACKGROUND

Cephalosporins

In 1948, the Italian physician Giuseppe Brotzu demonstrated that cultures of the fungus *Cephalosporium acremonium* exhibited bactericidal activity against the causative pathogen of typhoid fever (3) (original published paper: http://pacs.unica.it/brotzu/brotzuen.pdf). From these cultures, Newton and Abraham isolated cephalosporin C and characterized its molecule, containing a 7-aminocephalosporanic acid (7-ACA) nucleus, structurally and functionally analogous to the penicillin nucleus, and thus able to interfere with the synthesis of the prokaryotic cell wall by inactivation of DD-transpeptidase, the bacterial enzyme catalyzing the murein cross-linkage reaction (4).

Modification of the side chains of the original 7-ACA nucleus generated over the span of over five decades a remarkably diverse class of drugs, traditionally divided into first-, second-, third-, fourth- and now fifth-generation agents. In general, modification of the C-7 side

Scheme 2. Synthesis of Intermediate (IV)



chain of 7-ACA can modulate the spectrum of antibacterial activity of the cephalosporin, whereas changes in the substituent at position 3 can affect the pharmacokinetic properties, the penetration into bacterial cells and the target binding capacity of the drug. An aminothiazolyloximine substituent at position 7 of the 7-ACA nucleus (a methoxyimyl-5-aminothiazol moiety in fourth-generation agents) is a distinctive structural feature of most third- and fourth-generation cephalosporins. Fourth-generation cephalosporins have a positively charged quaternary ammonium group at the C-3′ position, a feature absent in third-generation agents, with the exception of ceftazidime (5).

Third-generation agents like ceftriaxone, ceftazidime and cefotaxime are among the most commonly prescribed cephalosporins. Cefotaxime, cefoperazone and ceftizoxime have the most pronounced activity against susceptible staphylococci. Compared to previously developed compounds, all third-generation cephalosporins show an expanded spectrum of activity against Gram-negative bacilli and in particular against most *Enterobacteriaceae,* with some notable exceptions (e.g., *Enterobacter cloacae)*. They are also active against gonococci, although decreased gonococcal sensitivity towards third-generation cephalosporins as a result of multiple mutations –of which the mosaic PBP2 is the most prominent representative– is becoming a worrisome clinical threat (6). Only two third-generation agents, ceftazidime and cefoperazone, are strongly active against *Pseudomonas aeruginosa*.

Functionally, fourth-generation agents are characterized by a broadened spectrum of activity, extended to a greater number of Gram-negative pathogens, compared to third-generation molecules. Enhanced activity has also been shown toward Gram-positive cocci, and in particular against penicillin-resistant *S. pneumoniae* (7). In general, all fourth-generation cephalosporins (e.g., cefepime, cefpirome) are active against *P. aeruginosa*.

P. aeruginosa

Due to its innate resistance, as well as reduced susceptibility, to multiple antimicrobial agents and to its ability to develop acquired multidrug resistance, the Gram-negative, opportunistic, nonfermenting pathogen *P. aeruginosa* is a leading cause of life-threatening nosocomial infections (8-10). *P. aeruginosa* is frequently isolated in hospital-acquired bacteremia and pneumonia, as well as intra-abdominal, urogenital (including urosepsis), wound and burn infections (11, 12). In addition, the ability of this pathogen to switch from a planktonic to a sessile way of life and to generate quorum sensing-regulated biofilms on biological or artificial substrates can further decrease the bactericidal activity and clinical efficacy of available antipseudomonal agents (13-15). Highly virulent *P. aeruginosa* possesses a type III secretion system, able to directly inject bacterial cytotoxins responsible for extensive damage to host cells and tissues (16).

For many years, treatment recommendations and therapeutic guidelines have been based on the combination of a β-lactam antibiotic with an aminoglycoside or a fluoroquinolone, and current therapeutic regimens still include antipseudomonal agents such as fluoroquinolones or aminoglycosides, carbapenems, monobactams, third-generation cephalosporins such as ceftazidime, and the penicillin derivative piperacillin combined with the β-lactamase inhibitor tazobactam (17). However, the emergence of multidrug-resistant and pan-resistant strains of *P. aeruginosa* has greatly reduced the clinical efficacy of many of these agents. Moreover, with the excep-

tion of doripenem, no new antipseudomonal agent has been released to the market in the last few years, and very few drugs are currently in the pipeline.

Resistance to *P. aeruginosa* varies from country to country. Whereas carbapenems and penicillins with β-lactamase inhibitors remain relatively active, fluoroquinolones and aminoglycosides have lost up to 80% of their specific activity in certain regions (18, 19). More recently, the old neuro- and nephrotoxic agents polymyxin B and colistin have been adopted as "last resort" antibiotics against multidrug-resistant pseudomonal infections. Regretfully, it appears that polymyxins will have a short life in our armamentarium: Fernandez et al. recently reported the emergence of adaptive resistance to polymyxins in *P. aeruginosa* via a novel ParR-ParS resistance regulator (20).

The determinants of acquired chemoresistance in *P. aeruginosa* are numerous. Loss of OprD channels is known to decrease the susceptibility to carbapenems, whereas activation of efflux pump systems can affect the permeability of bacterial cells to multiple antimicrobial agents. In addition, mutations of genes encoding for drug targets, such as *gyrA, gyrB, parC* or *parE*, can decrease the activity of fluoroquinolones (21-23). Resistance to β-lactam antibiotics, more frequently occurring in strains of the pathogen showing a mutator phenotype coselecting with resistance (24, 25), is based on the overexpression of the chromosomal cephalosporinase AmpC, that may occur via inactivation of the DD-endopeptidase PBP4 (26).

Transferable resistance determinants encoding extended-spectrum β-lactamases or metallo-β-lactamases are increasingly found in *P. aeruginosa* isolates worldwide. The increasing prevalence of multidrug-resistant strains coproducing β-lactamase enzymes of diverse mechanisms is also being reported in some countries (27-29). To counteract the catastrophic rise of multidrug or pan-resistance in *P. aeruginosa*, new drugs or treatment strategies are currently being developed, including new specific antipseudomonal β-lactams, like the 3-(2,4-disubstituted 3-aminopyrazolio)methyl cephalosporin CXA-101 (FR-264205), new combinations of β-lactamase inhibitors with established β-lactams, new antimicrobial peptides and peptide mimetics, new efflux pump inhibitors, new virulence modulators and new siderophore β-lactam uptake facilitators (30). BAL-30376, a novel triple combination comprising the siderophore monobactam BAL-19764, BAL-29880, a bridged monobactam-specific inhibitor of class C β-lactamases, and the class A β-lactamase inhibitor clavulanic acid, belongs to the latter group. The novel siderophore monobactam is expected to enter Gram-negative bacteria via non-porin routes involved in iron uptake, potentially also overcoming impermeability and overwhelming efflux (31).

Figure 1 shows the structure of ceftazidime, the most representative third-generation antipseudomonal cephalosporin. In CXA-101, at the C-7 position of the cephem ring, the aminothiazolyloximine residue, typical of third-generation compounds, has been modified to an aminothiadiazolyloximino substituent. An α-dimethylacetic acid moiety is attached to the *syn*-oxime oxygen, as in ceftazidime. Such a bulky acidic function attached to the oxime can enhance the antipseudomonal activity of cephalosporins, while retaining activity against *Enterobacteriaceae* (32).

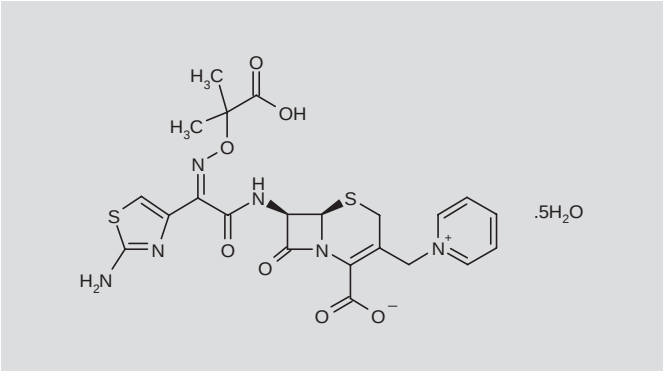


Figure 1. Structure of ceftazidime.

At the C-3 position of the cephem nucleus, the presence of a basic substituent ensures good permeability of CXA-101 into bacterial cells. A 2-methyl aminopyrazole substituent is attached to the cephem nucleus via a quaternary ammonium. This is a key feature, as ammonium cations confer to fourth-generation cephalosporins, and to the third-generation ceftazidime (a quaternary pyridine nitrogen in this case), increased activity against AmpC-type β-lactamase stably derepressed mutants in *P. aeruginosa* and *Enterobacteriaceae* (7, 33, 34).

At the C-4 position of the 2-methyl aminopyrazole a 1-(2-aminoethyl)carbamide substituent is attached. The optimization process leading to the choice of this group among various basic side chains was laborious. Initial attempts with a guanidine substituent resulted in a pK_a of 10.6 and an MIC of 1 μg/mL against a class C β-lactamase-producing strain of *P. aeruginosa*. However, the compound could not be further developed due to its strong convulsive effect in preclinical murine models (ED_{50} = 4.69 μg/head by intracerebroventricular administration) (34). This effect was attenuated by improving control of the alkalinity of the group, and 1-(2-aminoethyl)urea was found to be the most suitable substituent, showing the best balance between MIC against class C β-lactamase-producing *P. aeruginosa* strains, mean MIC against 54 clinically isolated strains and attenuated convulsive effect in mice compared to marketed cephems like ceftazidime.

PRECLINICAL PHARMACOLOGY

CXA-101 was discovered as a result of exploration of cephalosporin structure–activity relationships. Initial studies by Takeda and coworkers showed that CXA-101 was characterized by an antibacterial spectrum similar to ceftazidime, with MICs against *Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella pneumoniae and Haemophilus influenzae* of 32, 0.25, 0.0625 and 0.25 μg/mL, respectively (2). Importantly, the new compound was more potent not only against ciprofloxacin- or imipenem-resistant *P. aeruginosa*, but also against *P. aeruginosa* strains resistant to ceftazidime. As shown in a subsequent study by the same group, the MIC of CXA-101 at which 90% of 193 clinical isolates of *P. aeruginosa* were inhibited was 1 μg/mL, and CXA-101 was shown to be at least 16-fold more potent than tested comparators. Classical β-lactamases had limited influence on the MIC of CXA-101 or ceftazidime. However, the activity of CXA-101 was affected by extended-spectrum β-lactamases (ESBLs) like TEM-3, -4 and -8 and SHV-2, -3 and -4. A study per-

formed on a panel of 10 well-established ESBL-producing *P. aeruginosa* strains ($ESBL_A$, 9 strains, $ESBL_{M-D}$, 1 strain) showed that CXA-101 was active against four $ESBL_A$-producing strains (MICs ≤ 4 μg/mL), whereas all isolates except one were resistant to ceftazidime. The addition of 4 μg/mL tazobactam extended the activity against the one $ESBL_{M-D}$-producing isolate tested (MIC = 8 μg/mL). In comparison, imipenem was active against 9 of 10 isolates, ceftazidime-clavulanate against 4 of 10 isolates, piperacillin-tazobactam against 3 of 10 isolates, cefepime against 2 of 10 isolates and ceftazidime alone or ceftazidime-tazobactam against 1 of 10 isolates (35).

Similar to ceftazidime and imipenem, CXA-101 was not active against metallo-β-lactamase-producing strains, confirming that the drug is mainly active against mutation-evoked resistance mechanisms. As far as alternative resistance mechanisms were concerned, expression of efflux pumps had no effect on the MIC of CXA-101, but increased the MIC of ciprofloxacin 16-fold. In addition, CXA-101 was shown to be a poor inducer of chemoresistance compared to ceftazidime, imipenem and ciprofloxacin, as demonstrated by the low spontaneous mutation selection rates and by the limited reduction of susceptibility induced after serial culture passages (final MIC = 2 μg/mL). The lack of crossresistance between CXA-101 and ceftazidime or imipenem was initially attributed to the increased stability of the former against ampC β-lactamases (2). This hypothesis was investigated in a subsequent study, demonstrating, in a PAO1 ampD-deficient strain containing partially derepressed AmpC, that CXA-101 shows markedly decreased affinity for the enzyme (K_m = 120 μM) compared to ceftazidime (K_m = 6 μM) (36). In addition to this finding, CXA-101 was shown to be a very weak inducer of AmpC expression, and to be a more potent inhibitor of PBP1b, 1c, 2 and 3 compared to ceftazidime (37). In the same study, it was shown that CXA-101 shows a 15-fold reduced affinity for PBP4 compared to imipenem.

The activity of CXA-101 was tested by Livermore and coworkers against a panel of very diverse strains of *P. aeruginosa* and *Burkholderia cepacia*, a pathogen frequently involved in cystic fibrosis (CF). The *P. aeruginosa* strains included: 1) laboratory constructs (AmpC and OprD mutants); 2) PU21 transconjugants; 3) wild-type strains expressing metallo- and VEB-β-lactamases; 4) clinical isolates graded by intrinsic, efflux-mediated resistance; and 5) highly resistant CF isolates. *B. cepacia* was also isolated from CF patients (38). In summary, MICs for *P. aeruginosa* harboring fully derepressed AmpC were 4 μg/mL for CXA-101, 64 μg/mL for ceftazidime and 2 μg/mL for imipenem. PU21 transconjugants were more susceptible to CXA-101 (MIC = 0.5 μg/mL) than to ceftazidime (MIC = 2 μg/mL). ESBL OXA-15, -11, -14 and -16 mutants, as well as the PER-1 β-lactamase, caused resistance to both cephalosporins (MIC > 32 μg/mL), but resistance of *P. aeruginosa* expressing PER-1 was fully reversed by exposure to 4 μg/mL clavulanate (CXA-101 MIC = 0.5 μg/mL). IMP-type and VIM-type metallo-β-lactamases rendered *P. aeruginosa* clinical isolates resistant to both CXA-101 (MIC = 128 μg/mL) and ceftazidime (MIC > 32 μg/mL). In clinical isolates characterized by increasing efflux-mediated resistance, MICs of CXA-101 showed parallel increasing trends, but remained 2- to 8-fold lower than the MICs of ceftazidime. More than half (57%) of 56 highly challenging CF isolates were resistant to ceftazidime at the CLSI/EUCAST breakpoint of 8 μg/mL. CXA-101 performed better, as only 36% of strains showed resistance at the same breakpoint. In general, the MICs of CXA-101 for these isolates were 2- to -8-fold lower than those of ceftazidime. MICs of CXA-101 and ceftazidime were comparable when tested against CF isolates of *B. cepacia*.

The activity of CXA-101 against *P. aeruginosa* isolates from CF patients was also investigated by Zamorano and coworkers (39). A collection of 100 isolates was obtained from 50 chronic CF patients. From each patient an "early" and a "late" specimen were collected; the average time lag between sampling was 67 months. CXA-101 was tested in comparison with a large panel of antipseudomonal agents. An increasing trend for MICs was observed between the first and the last isolates collected for all tested antibacterial agents. In general, CXA-101 was more potent than imipenem, ceftazidime, cefepime, piperacillin-tazobactam, levofloxacin and tobramycin. The activity of CXA-101 was comparable to meropenem. CXA-101 was active against a high proportion of isolates resistant to all other tested antibacterial agents, with MIC_{50} values of 1-2 μg/mL. Importantly, CXA-101 was active against multidrug-resistant *P. aeruginosa* strains, with MIC_{50} and MIC_{90} values of 2 and 16 μg/mL, respectively, and the vast majority of multidrug-resistant isolates (84%) showed CXA-101 MICs inferior to the 8 μg/mL breakpoint. Interestingly, CXA-101 was the only tested antibiotic retaining a comparable potency against "early" and "late" isolates. Notably, 51 of the 100 isolates from this study showed a mucoid phenotype and 19 a small-colony phenotype. CXA-101 and meropenem were the most potent agents against strains exhibiting these phenotypes (28).

Loss-of-function mutations of the anti-sigma factor mucA, an inhibitor of AlgT-dependent transcription, is responsible for mucoidy in *P. aeruginosa* colonizing the airways of CF patients (40, 41). In isogenic derivatives of the PAO1 *Pseudomonas* strain defective in mucA and/or mutS, Riera et al. demonstrated that, compared to ceftazidime, meropenem and ciprofloxacin, CXA-101 showed the highest biofilm bactericidal activity at 1 x the MIC for wild-type, mucoid and hypermutable strains of the pathogen (42). In addition, mutant frequencies lower than 5×10^{-11} were observed, whereas at four times the MIC ceftazidime, meropenem and ciprofloxacin were in the 10^{-7} range in PAO1, or between 7.3×10^{-4} and 1.3×10^{-5} in the PAOMS derivative strains.

Infections caused by multidrug-resistant strains of *P. aeruginosa* represent a major therapeutic challenge today. Bulik and coworkers recently exposed to CXA-101 a panel of *P. aeruginosa* isolates showing a multidrug resistance phenotype selected from a collection of 408 nongenotyped *P. aeruginosa* isolates from the respiratory tract. Isolates were collected from 40 U.S. hospitals (43). The majority of multidrug-resistant isolates (63%) showed MICs for CXA-101 inferior to 4 μg/mL. The MIC_{50} of CXA-101 and imipenem/meropenem was 2 and 16 μg/mL, respectively. Non-multidrug-resistant isolates from the same collection were resistant to various agents. Interestingly, in carbapenem-resistant isolates (MIC_{90} = 32 μg/mL), CXA-101 showed an MIC_{90} of 8 μg/mL. Tazobactam did not improve the activity of CXA-101 against multidrug-resistant *P. aeruginosa* strains.

The activity of CXA-101 was also tested against a panel of multidrug-resistant *P. aeruginosa* strains by Juan and coworkers (44). The multidrug-resistant isolates tested represented 42% of a collection of a total of 236 non-CF, carbapenem-resistant *P. aeruginosa* clinical isolates from Spanish medical centers. The MIC_{50}/MIC_{90} of CXA-101 for the entire collection of carbapenem-resistant *P. aeruginosa* isolates,

including the multidrug-resistant subgroup and a panel of AmpC-hyperproducing clones (53% of total isolates), was 1/4 µg/mL, with 95.3% of the isolates showing an MIC < 8 µg/mL. In comparison, the MIC_{50}/MIC_{90} of ceftazidime was 8/64 µg/mL. Crossresistance with a large group of comparator antipseudomonal agents (imipenem, meropenem, ceftazidime, cefepime, piperacillin with/without tazobactam, aztreonam, gentamicin, tobramycin, amikacin, ciprofloxacin) was not evidenced. Against 11 multidrug-resistant strains CXA-101 showed an MIC superior to the 8 µg/mL breakpoint. Decreased susceptibility to CXA-101 of 10 of these strains was found to be due to transferable resistance determinants, including the metallo-β-lactamase VIM-2 (one strain) and the ESBLs PER-1, OXA-101, OXA-17, OXA-144 (a new OXA-2 derivative), as well as the new BEL-3 variant.

The data summarized above, obtained from independent studies involving highly resistant and highly challenging strains, are very encouraging. The potential of CXA-101 as a promising agent in complicated pseudomonal infections is further confirmed by a study performed on a highly challenging collection of in vitro-selected β-lactam-resistant *P. aeruginosa* mutants harboring multiple combinations of mutations leading to various levels of AmpC overexpression (*ampD*, *ampDh2*, *ampDh3* and PBP4-encoding *dacB*) and oprD porin loss (45). CXA-101 was active against all single and combined mutations causing AmpC hyperproduction. CXA-101 MICs were not modified by *ampD* inactivation (MIC = 0.5 µg/mL), and the inactivation of multiple (two or three) *ampD* or *dacB* genes produced a minor increase in the MIC (1 µg/mL). A double AmpD-PBP4 mutant showing *ampC* hyperexpression was resistant to ceftazidime and cefepime, but showed an MIC of 2 µg/mL when exposed to CXA-101.

In the context of the same study, CXA-101 was shown to be very active against a panel of 50 clinical *P. aeruginosa* mutants showing β-lactam or fluoroquinolone resistance, generated during antipseudomonal treatment of intensive care unit patients. MICs ranged between 0.125 and 4 µg/mL against AmpC-hyperproducing mutants and high-level β-lactam-resistant AmpD-PBP4 double mutants, even when these expressed the MexAB-OprM efflux protein (45).

The cephalosporin CXA-101 is being developed and will likely be marketed in combination with the β-lactamase inhibitor tazobactam under the name CXA-201. This combination was recently shown to be active against AmpC-hyperproducing *Enterobacteriaceae* (46). However, the therapeutic potential of the CXA-101-tazobactam combination against ESBL-producing *Enterobacteriaceae* and *P. aeruginosa* has not been defined with certainty, and perhaps needs to be thoroughly characterized. In the report by Livermore et al., 14 (23%) of a total of 59 ESBL producers (harboring CTX-M, SHV and TEM type enzymes) were resistant to the 8+4 µg/mL combination, but only 4 retained resistance upon exposure to the 8+8 µg/mL combination.

In the report by Juan et al. described above (44), the activity of 8+4 or 8+8 µg/mL combinations was tested against 11 isolates showing MICs to CXA-101 superior to 8 µg/mL. Eight isolates (of which four were positive in the DDST test) were producers of OXA-17, -144, -101 and BEL-3. Only in two cases (both expressing the OXA-144 ESBL) was the CXA-101 MIC of 32 µg/mL reduced to 8 µg/mL in the presence of the highest tested dose of tazobactam (8 µg/mL).

Table I summarizes some of the susceptibility data described above for CXA-101 and various comparators.

The study by Takeda et al. described above included the assessment of the in vivo preclinical efficacy of CXA-101 against various experimental pseudomonal infections (2). Briefly, CXA-101 was shown to be: 1) equivalent to imipenem but better than ceftazidime in resolving pulmonary infections in murine models at the dose of 2 mg/kg; 2) significantly better than imipenem against urinary tract infections at doses as low as 0.5 mg/kg; and 3) better than either drug against burn wound pseudomonal infections (dose: 10 mg/kg).

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics of CXA-101 have been investigated in the frame of a phase I study involving a total of 64 healthy volunteers receiving single (Part 1 of the study) or multiple i.v. doses (Part 2 of the study) of CXA-101 (47). In Part 1, five cohorts of eight subjects each –six receiving the cephalosporin and two receiving placebo– were treated with single doses of 250, 500, 1000, 1500 and 2000 mg CXA-101 (infusion time: 1 h). In Part 2 of the study, 3 cohorts of 8 volunteers received thrice-daily doses of 500 or 1000 mg or twice-daily doses of 1500 mg CXA-101 for 10 days. Results were analyzed using noncompartmental modeling methods. In general, parameters did not appear to substantially differ from those of ceftazidime (48). Briefly, the C_{max} and AUC conserved linearity over the whole dose range, and CXA-101 exhibited dose-linear pharmacokinetics. Mean plasma half-lives were independent of dose and dosing duration, and ranged between 1.8 and 2.6 h. Because of the relatively short plasma half-life of CXA-101, Ge et al. estimated that a clinical dose regimen of 1000 mg every 8 h could be adopted for future clinical studies (47).

Drug accumulation was minimal upon multiple dosing regimens at all administered doses, as documented by minor changes in AUC values over the 10-day treatment period. Clearance was shown to be primarily renal and independent of dose and dosing regimen (102.4 mL/min after a single dose and 112.2 mL/min after the last of multiple doses). Plasma protein binding of CXA-101 is about 20%; the method by which this parameter was assessed has not been described in detail to the authors' knowledge. The volume of distribution of CXA-101 is approximately equal to the extracellular fluid volume (47).

Metabolic transformation of CXA-101 appears to be very limited, as 92.5% of the unmodified drug could be recovered in the urine of treated volunteers receiving a single dose of the antibiotic. The percentage of unmodified, renally excreted drug was slightly higher (95%) in patients treated with multiple doses of the drug. From this evidence, the investigators concluded that CXA-101 might be effective in the treatment of urinary tract infections caused by sensitive uropathogens, including *P. aeruginosa* (47).

It is known that "real-life" patient conditions may markedly affect the pharmacokinetic parameters of antibacterials, and in particular those of β-lactams showing short half-lives and limited metabolism. As recently reported by Georges et al., the distribution volume of ceftazidime can significantly increase –and the clearance of the antibiotic can significantly decrease– in intensive care unit patients when compared to healthy volunteers (49).

Table I. *Susceptibility data for CXA-101 and four representative antipseudomonal comparators against Pseudimonas aeruginosa strains and clinical isolates showing different resistance phenotypes.*

P. aeruginosa strain/isolate	CXA-101 MIC_{50}-MIC_{90} (mg/L)	Ceftazidime MIC_{50}-MIC_{90} (mg/L)	Imipenem MIC_{50}-MIC_{90} (mg/L)	Meropenem MIC_{50}-MIC_{90} (mg/L)	Piperacillin-Tazobactam MIC_{50}-MIC_{90} (mg/L)	Ref.
Isolates from cystic fibrosis patients	0.5-2	4-64	4-64	0.5-8	4-128	39
Carbapenem/multidrug-resistant clinical isolates	1-4	8-64	–	–	–	44
Multidrug-resistant clinical isolates	2/2[a]-> 64/> 64[a]	64-256	16-128	16-128	256-256	43
Imipenem-resistant clinical isolates	2/1[a]-8/8[a]	16-128	16-32	16-32	32-256	
Ceftazidime-resistant clinical isolates	4/2[a]-16/16[a]	64-256	4-32	4-32	256-256	
Piperacillin-tazobactam-resistant clinical isolates	2/1[a]-8/8[a]	32-128	2-32	4-32	64-256	
AmpC-hyperproducing isolates	1-4	–	–	–	–	45
Carbapenem-resistant clinical isolates	0.5-4	–	–	–	–	
Ceftazidime-resistant clinical isolates	1-4	–	–	–	–	
Piperacillin-tazobactam-resistant clinical isolates	1-4	–	–	–	–	
P. aeruginosa, susceptible clinical isolates	0.5-1	2-16	2-16	–	–	2
Ceftazidime-resistant clinical isolates	2-4	64-128	16-32	–	–	
Imipenem-resistant/ceftazidime-susceptible isolates	0.5-1	4-16	16-32	–	–	
Clinical isolates with IMP or VIM metallo-β-lactamases	> 128-> 128	64-> 128	> 64-> 64	–	–	38
	MIC or MIC range	MIC or MIC range	MIC	MIC	MIC	Ref.
PAO1 strain	0.5	2	2	0.5	2	45
PAO1 *ampD* knockout mutant	0.5	8	2	2	16	
PAO1 *dacB* (PBP4) knockout mutant	1	32	2	0.5	64	
PAO1 *ampD+dacB* double knockout mutant	2	128	2	2	256	
PAO1 *oprD* spontaneous mutant	0.5	2	16	1	2	
PAO1 *oprD+dacB* double mutant	0.5	32	16	4	64	
GW-1 (GES-2 $ESBL_A$-producing) clinical isolate	> 64, > 64[a], > 64[b]	> 64	2	–	128	35
RNL-1 (PER-1 $ESBL_A$-producing) clinical isolate	> 64, 32[a], 32[b]	> 64	1	–	8	
1782 (SHV-5 $ESBL_A$-producing) clinical isolate	4, 1[a], 1[b]	> 64	2	–	64	
PG13 (OXA-32 $ESBL_{M\text{-}D}$-producing) clinical isolate	> 64, 8[a], 8[b]	64	16	–	16	
22029 strain (metallo-β-lactamase producer)	> 128	> 128	128	–	–	2
FP1380 strain (constitutive *ampC* producer)	4	> 128	0.5	–	–	
PAO4069 strain (inducible *ampC* producer)	0.5	2	1	–	–	
ampC-inducible or -deficient *P. aeruginosa* expression variants	0.5-1	2-4	2 (inducible), ≤ 0.025 (deficient)	–	–	38
Fully ampC-derepressed *P. aeruginosa* expression variants	4	64-128	2	–	–	
VEB ESBL-producing isolates	> 128, 2[c]	> 128	2	–	–	

[a]Combined with 4 mg/L tazobactam; [b]combined with 8 mg/L tazobactam; [c]combined with 4 mg/L clavulanate.

Because CXA-101, like ceftazidime, is predominantly excreted via the kidneys, further studies exploring the pharmacokinetics of the new cephalosporin in a variety of severe conditions (e.g., in case of compromised renal function) will greatly help to better characterize the dosing profile of CXA-101 in complicated cases.

SAFETY

The phase I study by Ge et al. described above included safety and tolerability endpoints (47). CXA-101 appears to be well tolerated and characterized by a favorable safety profile. All 64 volunteers enrolled completed the study, none withdrawing due to adverse events and no dose-limiting toxicities being recorded. Mild, non-treatment-limiting pain or erythema at the infusion site occurred in the multiple-dose CXA-101 group, but also in placebo-treated subjects, albeit at a lower frequency. Biochemical, hematological, urinalysis and coagulation parameters were unaffected by treatment, and no clinically significant ECG finding was reported.

Paresthesia and headache were reported in two cases in the single-dose placebo group. Abdominal pain, nausea, somnolence and headache were reported in four of six patients treated with single-

dose CXA-101 (1000 mg). During the multiple-dose study, two cases of diarrhea, one of hypoesthesia and one of paresthesia were recorded in the 500 mg thrice daily group, but not at higher doses of the drug. One flushing episode was recorded in the 1000 mg thrice daily group.

CLINICAL STUDIES

A randomized, comparative, double-blind, multicenter trial designed to assess the safety and both the microbiological and the clinical outcomes of administration of CXA-101 in complicated urinary tract infections (cUTIs) has recently been completed (50). Complicated UTIs are frequently caused by highly resistant nosocomial pathogens, and often require prolonged courses of treatment with a limited choice of active agents (51). One hundred and twenty-nine adult patients were enrolled in the trial. Eighty-six intent-to-treat (ITT) patients were randomized to receive CXA-101 1000 mg i.v. thrice daily and 43 received ceftazidime 1000 mg thrice daily for 7-10 days. Microbiological and clinical outcomes were evaluated at the test-of-cure visit, performed 6-9 days after the end of therapy. Safety data from this study seem to confirm the findings of the phase I trial described above (47). CXA-101 was generally well tolerated, as no patients discontinued treatment due to adverse events (AEs) or laboratory abnormalities. The incidence and pattern of AEs were similar in the two treatment groups; 3% severe AEs were reported. A relapse of pyelonephritis (not considered a treatment failure by the authors) was the only serious AE occurring during the phase II study.

Microbiological cure rates in a "microbiologically evaluable" population of a total of 82 patients treated with CXA-101 and ceftazidime (CXA-101: n = 55; ceftazifdime: n = 27) were 85.5% and 92.6%, respectively. Eradication rates in subjects with *Escherichia coli,* the most common pathogen, were 91.7% and 94.7%, respectively, in the CXA-101 and ceftazidime groups. Clinical response rates in the modified ITT population of a total 127 patients were 91% and 92%, respectively, with CXA-101 and ceftazidime. Sustained clinical cure rates at the late follow-up visit (3-4 weeks after therapy) were 98% for CXA-101 and 92.6% for ceftazidime (50).

P. aeruginosa was isolated only in patients randomized to the CXA-101 arm; therefore, comparative data are not available. However, microbiological results were comparable to those in other recent studies of *P. aeruginosa* in cUTIs (Cubist Pharmaceuticals Press Release: http://www.snl.com/irweblinkx/file.aspx?IID=4093793&FID=9771773).

CXA-201, an association of CXA-101 and tazobactam, is currently being tested in the frame of a multicenter, double-blind, randomized study with meropenem as active comparator in patients affected by complicated intra-abdominal infections. Results of this trial are expected by mid-2011 (Cubist Pharmaceuticals Press Release: http://www.snl.com/irweblinkx/file.aspx?IID=4093793&FID=9771773).

DRUG INTERACTIONS

Little information is available about drug–drug interactions involving CXA-101. In the report describing the results of the CXA-101 pharmacokinetic study, Ge and coworkers emphasized that the absence of any interaction with known hepatic metabolic pathways provided confidence in a low likelihood of cytochrome P450-dependent drug–drug interactions (47).

CONCLUSIONS

In light of the rapid increase in resistance of *P. aeruginosa* clinical strains against most suitable antibiotic substances, such as carbapenems and fluoroquinolones, antibiotics active against *Pseudomonas* are highly welcome. Current available data on CXA-101 are promising and endorse further clinical development of this agent. There are, however, missing data regarding collateral effects, for example the propensity of CXA-101 to select for ESBL-producing Gram-negatives. Results of the clinical studies performed will soon be available for publication and thus increase the current limited information on CXA-101.

SOURCES

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DISCLOSURES

Dr. Naber has acted as an investigator, consultant, speaker at scientific meetings and has prepared scientific publications on behalf of Bionorica, Daiichi Sankyo, MerLion, OM Pharma, Johnson & Johnson/Janssen-Cilag, Pierre Fabre, sanofi-aventis, Rosen Pharma and Zambon. Dr. Wagenlehner participated in the the phase II study "CXA-101 in Complicated UTI". Dr. Perletti has acted as a consultant for Astellas Pharma in 2010. Dr. Magri states no conflicts of interest.

REFERENCES

1. Ohki, H., Yamanaka, T., Toda, A. et al. (Astellas Pharma, Inc.; Wakunaga Pharmaceutical Co., Ltd.). *Cephem compounds*. EP 1556389, JP 2006506459, US 7129232, US 2007037786, WO 2004039814.
2. Toda, A., Ohki, H., Yamanaka, T. et al. *Synthesis and SAR of novel parenteral anti-pseudomonal cephalosporins: Discovery of FR264205.* Bioorg Med Chem Lett 2008, 18(17): 4849-52.
3. Bo, G. *Giuseppe Brotzu and the discovery of cephalosporins*. Clin Microbiol Infect 2000, 6(Suppl. 3): 6-9.
4. Newton, G.G., Abraham E.P. *Isolation of cephalosporin C, a penicillin-like antibiotic containing D-alpha-aminoadipic acid*. Biochem J 1956, 62(4): 651-8.
5. Klein, N.C., Cunha, B.A. *Third-generation cephalosporins.* Med Clin North Am 1995, 79(4): 705-19.
6. Tapsall, J.W. *Neisseria gonorrhoeae and emerging resistance to extended spectrum cephalosporins.* Curr Opin Infect Dis 2009, 22(1): 87-91.
7. Garau, J. *The clinical potential of fourth-generation cephalosporins.* Diagn Microbiol Infect Dis 1998, 31(3): 479-80.
8. Obritsch, M.D., Fish, D.N., MacLaren, R., Jung, R. *Nosocomial infections due to multidrug-resistant Pseudomonas aeruginosa: Epidemiology and treatment options.* Pharmacotherapy 2005, 25(10): 1353-64.
9. Livermore, D.M., Woodford, N. *The beta-lactamase threat in Enterobacteriaceae, Pseudomonas and Acinetobacter.* Trends Microbiol 2006;14(9): 413-20.
10. Driscoll, J.A., Brody, S.L., Kollef, M.H. *The epidemiology, pathogenesis and treatment of Pseudomonas aeruginosa infections.* Drugs 2007, 67(3): 351-68.

11. El Solh, A.A., Alhajhusain, A. *Update on the treatment of Pseudomonas aeruginosa pneumonia.* J Antimicrob Chemother 2009, 64(2): 229-38.
12. van Delden, C. *Pseudomonas aeruginosa bloodstream infections: How should we treat them?* Int J Antimicrob Agents 2007, 30(Suppl. 1): S71-5.
13. Winstanley, C., Fothergill, J.L. *The role of quorum sensing in chronic cystic fibrosis Pseudomonas aeruginosa infections*. FEMS Microbiol Lett 2009, 290(1): 1-9.
14. Kirisits, M.J., Parsek, M.R. *Does Pseudomonas aeruginosa use intercellular signalling to build biofilm communities?* Cell Microbiol 2006, 8(12): 1841-9.
15. Hill, D., Rose, B., Pajkos, A. et al. *Antibiotic susceptabilities of Pseudomonas aeruginosa isolates derived from patients with cystic fibrosis under aerobic, anaerobic, and biofilm conditions.* J Clin Microbiol 2005, 43(10): 5085-90.
16. Hauser, A.R. *The type III secretion system of Pseudomonas aeruginosa: infection by injection.* Nat Rev Microbiol 2009, 7(9): 654-65.
17. Giamarellou, H., Kanellakopoulou, K. *Current therapies for pseudomonas aeruginosa.* Crit Care Clin 2008, 24(2): 261-78.
18. Turner, P.J. *MYSTIC Europe 2007: Activity of meropenem and other broad-spectrum agents against nosocomial isolates.* Diagn Microbiol Infect Dis 2009, 63(2): 217-22.
19. Walsh, F., Bracher, S., Turner, P., Amyes, S.G. *Epidemiological analysis of carbapenem-sensitive and -resistant Pseudomonas aeruginosa.* J Hosp Infect 2005, 60(3): 240-4.
20. Fernandez, L., Gooderham, W.J., Bains, M., McPhee, J.B., Wiegand, I., Hancock, R.E. *Adaptive resistance to the "last hope" antibiotics polymyxin B and colistin in Pseudomonas aeruginosa is mediated by the novel two-component regulatory system ParR-ParS.* Antimicrob Agents Chemother 2010, 54(8): 3372-82.
21. Livermore, D.M. *Interplay of impermeability and chromosomal beta-lactamase activity in imipenem-resistant Pseudomonas aeruginosa.* Antimicrob Agents Chemother 1992, 36(9): 2046-8.
22. Aeschlimann, J.R. *The role of multidrug efflux pumps in the antibiotic resistance of Pseudomonas aeruginosa and other gram-negative bacteria. Insights from the Society of Infectious Diseases Pharmacists.* Pharmacotherapy 2003, 23(7): 916-24.
23. Piddock, L.J. *Mechanisms of fluoroquinolone resistance: An update 1994-1998.* Drugs 1999, 58(Suppl. 2): 11-8.
24. Oliver, A., Canton, R., Campo, P., Baquero, F., Blazquez, J. *High frequency of hypermutable Pseudomonas aeruginosa in cystic fibrosis lung infection.* Science 2000, 288(5469): 1251-3.
25. Henrichfreise, B., Wiegand, I., Luhmer-Becker, I., Wiedemann, B. *Development of resistance in wild-type and hypermutable Pseudomonas aeruginosa strains exposed to clinical pharmacokinetic profiles of meropenem and ceftazidime simulated in vitro.* Antimicrob Agents Chemother 2007, 51(10): 3642-9.
26. Moya, B., Doetsch, A., Juan, C., Blazquez, J., Zamorano, L., Haussler, S., Oliver, A. *Beta-lactam resistance response triggered by inactivation of a nonessential penicillin-binding protein.* PLoS Pathog 2009, 5(3): e1000353.
27. Upadhyay, S., Sen, M.R., Bhattacharjee, A. *Presence of different beta-lactamase classes among clinical isolates of Pseudomonas aeruginosa expressing AmpC beta-lactamase enzyme.* J Infect Dev Ctries 2010, 4(4): 239-42.
28. Rodriguez-Martinez, J.M., Poirel, L., Nordmann, P. *Extended-spectrum cephalosporinases in Pseudomonas aeruginosa.* Antimicrob Agents Chemother 2009, 53(5): 1766-71.
29. Poirel, L., Docquier, J.D., De Luca, F., Verlinde, A., Ide, L., Rossolini, G.M., Nordmann, P. *BEL-2, an extended-spectrum beta-lactamase with increased activity toward expanded-spectrum cephalosporins in Pseudomonas aeruginosa.* Antimicrob Agents Chemother 2010, 54(1): 533-5.
30. Page, M.G., Heim, J. *Prospects for the next anti-Pseudomonas drug.* Curr Opin Pharmacol 2009, 9(5): 558-65.
31. Livermore, D.M., Mushtaq, S., Warner, M. *Activity of BAL30376 (monobactam BAL19764 + BAL29880 + clavulanate) versus Gram-negative bacteria with characterized resistance mechanisms.* J Antimicrob Chemother 2010, 65(11): 2382-95.
32. Dunn, G.L. *Ceftizoxime and other third-generation cephalosporins: Structure-activity relationships.* J Antimicrob Chemother 1982, 10(Suppl. C): 1-10.
33. Wilson, W.R. *The role of fourth-generation cephalosporins in the treatment of serious infectious diseases in hospitalized patients.* Diagn Microbiol Infect Dis 1998, 31(3): 473-7.
34. Takeda, S., Nakai, T., Wakai, Y., Ikeda, F., Hatano, K. *In vitro and in vivo activities of a new cephalosporin, FR264205, against Pseudomonas aeruginosa.* Antimicrob Agents Chemother 2007, 51(3): 826-30.
35. Giske, C.G., Ge, J., Nordmann, P. *Activity of cephalosporin CXA-101 (FR264205) and comparators against extended-spectrum-{beta}-lactamase-producing Pseudomonas aeruginosa.* J Antimicrob Chemother 2009, 64(2): 430-1.
36. Takeda, S., Ishii, Y., Hatano, K., Tateda, K., Yamaguchi, K. *Stability of FR264205 against AmpC beta-lactamase of Pseudomonas aeruginosa.* Int J Antimicrob Agents 2007, 30(5): 443-5.
37. Moya, B., Zamorano, L., Juan, C., Ge, Y., Oliver, A. *Affinity of the new cephalosporin CXA-101 to penicillin-binding proteins of Pseudomonas aeruginosa.* Antimicrob Agents Chemother 2010, 54(9): 3933-7.
38. Livermore, D.M., Mushtaq, S., Ge, Y., Warner, M. *Activity of cephalosporin CXA-101 (FR264205) against Pseudomonas aeruginosa and Burkholderia cepacia group strains and isolates.* Int J Antimicrob Agents 2009, 34(5): 402-6.
39. Zamorano, L., Juan, C., Fernandez-Olmos, A., Ge, Y., Canton, R., Oliver, A. *Activity of the new cephalosporin CXA-101 (FR264205) against Pseudomonas aeruginosa isolates from chronically infected cystic fibrosis patients.* Clin Microbiol Infect, Epub ahead of print.
40. Xie, Z.D., Hershberger, C.D., Shankar, S., Ye, R.W., Chakrabarty, A.M. *Sigma factor-anti-sigma factor interaction in alginate synthesis: inhibition of AlgT by MucA.* J Bacteriol 1996, 178(16): 4990-6.
41. Hassett, D.J., Sutton, M.D., Schurr, M.J., Herr, A.B., Caldwell, C.C., Matu, J.O. *Pseudomonas aeruginosa hypoxic or anaerobic biofilm infections within cystic fibrosis airways.* Trends Microbiol 2009, 17(3): 130-8.
42. Riera, E., Macià, M.D., Mena, A., Mulet, X., Pérez, J.L., Ge, Y., Oliver, A. *Anti-biofilm and resistance suppression activities of CXA-101 against chronic respiratory infection phenotypes of Pseudomonas aeruginosa strain PAO1.* J Antimicrob Chemother 2010, 65(7): 1399-404.
43. Bulik, C.C., Christensen, H., Nicolau, D.P. *In vitro potency of CXA-101, a novel cephalosporin, against Pseudomonas aeruginosa displaying various resistance phenotypes, including multidrug resistance.* Antimicrob Agents Chemother 2010, 54(1): 557-9.
44. Juan, C., Zamorano, L., Perez, J.L., Ge, Y., Oliver, A.; Spanish Group for the Study of Pseudomonas; Spanish Network for Research in Infectious Diseases. *Activity of a new antipseudomonal cephalosporin, CXA-101 (FR264205), against carbapenem-resistant and multidrug-resistant Pseudomonas aeruginosa clinical strains.* Antimicrob Agents Chemother 2010, 54(2): 846-51.
45. Moya, B., Zamorano, L., Juan, C., Perez, J.L., Ge, Y., Oliver, A. *Activity of a new cephalosporin, CXA-101 (FR264205), against beta-lactam-resistant*

Pseudomonas aeruginosa mutants selected in vitro and after antipseudomonal treatment of intensive care unit patients. Antimicrob Agents Chemother 2010, 54(3): 1213-7.

46. Livermore, D.M., Mushtaq, S., Ge, Y. *Chequerboard titration of cephalosporin CXA-101 (FR264205) and tazobactam versus beta-lactamase-producing Enterobacteriaceae.* J Antimicrob Chemother 2010, 65(9): 1972-4.
47. Ge, Y., Whitehouse, M.J., Friedland, I., Talbot, G.H. *Pharmacokinetics and safety of CXA-101, a new antipseudomonal cephalosporin, in healthy adult male and female subjects receiving single- and multiple-dose intravenous infusions.* Antimicrob Agents Chemother 2010, 54(8): 3427-31.
48. Tjandramaga, T.B., Van Hecken, A., Mullie, A., Verbesselt, R., De Schepper, P.J., Verbist, L. *Comparative pharmacokinetics of ceftazidime and moxalactam.* Antimicrob Agents Chemother 1982, 22(2): 237-41.
49. Georges, B., Conil, J.M., Seguin, T. et al. *Population pharmacokinetics of ceftazidime in intensive care unit patients: Influence of glomerular filtration rate, mechanical ventilation, and reason for admission.* Antimicrob Agents Chemother 2009, 53(10): 4483-9.
50. Umeh, O., Cebrik, D., Friedland I.R. *A double-blind, randomized, phase 2 study to compare the safety and efficacy of intravenous CXA-101 (CXA) and intravenous ceftazidime (CTZ) in complicated urinary tract infection (cUTI).* 50th Annu Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, Boston) 2010, Abst L1-361a.
51. Wagenlehner, F.M.E., Pilatz, A, Naber, K.G., Perletti, G., Wagenlehner, C.M., Weidner, W. *Anti-infective treatment of bacterial urinary tract infections.* Cur Med Chem 2008, 15(14): 1412-27.