Antimicrobial Report

Safety and efficacy of tigecycline to treat multidrug-resistant infections in paediatrics; an evidence synthesis.

Mike Sharland, MD[1], Keith A. Rodvold, PharmD[2], Hal R. Tucker, MD[3], Nathalie Baillon-Plot, MD[4], Margaret Tawadrous, MD[3], M. Anne Hickman, DVM, PhD[5], Susan Raber, PharmD [6], Joan M. Korth-Bradley, PharmD, PhD [3*], Humberto Díaz Ponce, MD[3], Michele Wible, MS[3]

[1]Paediatric Infectious Diseases Research Group, St. George's, University of London, UK; [2]College of Pharmacy and Medicine, University of Illinois at Chicago, IL, USA; [3]Pfizer Inc, Collegeville, PA, USA; *Clinical Pharmacology; [4]Pfizer PFE, Paris, France; [5]Worldwide Safety and Regulatory, Pfizer Inc, Groton, CT, USA; [6]Clinical Pharmacology, Pfizer Essential Health, Pfizer Inc, La Jolla, CA, USA

Correspondence: Mike Sharland, MD, Professor of Paediatric Infectious Diseases, St George's, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom. Tel: +44 (0)20 8725 3922; Email: mike.sharland@stgeorges.nhs.uk

Conflicts of Interest and Source of Funding

MS received no funding from Pfizer for this work. KAR received no funding from Pfizer for this work. HRT, NB-P, MT, MAH, SR, JMK-B, HD-P, and MW are Pfizer employees. This study was funded by Pfizer. Editorial support was provided by Thomas Gegeny of Engage Scientific Solutions and was funded by Pfizer.

Key words

pharmacokinetics, pharmacovigilance, real-world experience

Abbreviated title

Safety & efficacy of tigecycline for MDR infections in children

Running head title

Tigecycline for MDR infections in children

ABSTRACT

Background

The need for antimicrobial therapies effective against multidrug resistant (MDR) organisms for children remains unmet. Tigecycline shows antibacterial activity across a broad spectrum of bacteria and is approved for treating complicated skin and skin-structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and, in the US, community-acquired bacterial pneumonia (CAP) for adult patients. No blinded, randomized Phase 3 tigecycline clinical trials on neonates or children have been completed or planned. This review aimed to provide a comprehensive synthesis of all the existing data sources, both on-label and off-label, for tigecycline use in children.

Methods

Data on tigecycline use in children were identified from published and unpublished sources including clinical trials, expanded access and compassionate use programs, databases of healthcare records and patient safety monitoring.

Results

Pharmacokinetic simulations predicted that tigecycline 1.2 mg/kg (maximum dose 50 mg) every 12 hours (q12h) in children 8–11 years and 50 mg q12h in children 12–<18 years would achieve exposure similar to adults receiving 50 mg q12h. Available Phase 2 paediatric clinical trial data and data from other sources demonstrated similar clinical efficacy between adult and paediatric patients treated with tigecycline. These data showed no new or unexpected safety concerns with tigecycline in children.

Conclusions

Information presented here may help guide the appropriate use of tigecycline in children with MDR infections. Continued pharmacovigilance from real-world observational studies may also further refine appropriate use of tigecycline.

INTRODUCTION

A recent analysis reported that of 6.3 million children who died before age 5 years in 2013, just over half died from infectious causes.[1] Because of the spread of antibiotic-resistant bacteria, continued need exists for therapies effective against multidrug resistant (MDR) organisms, including among children and newborns, where MDR *Klebsiella* spp., *Acinetobacter* spp., and *Escherichia coli* cause significant morbidity and mortality.[2] Cystic fibrosis studies demonstrate growing rates of MDR infections caused by *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bulkholderia* species, *Stenotrophomonas maltophilia*,[3] and rapid growing mycobacteria.

Tigecycline, a semisynthetic tetracycline, has demonstrated antibacterial activity across a broad spectrum of Gram-positive, Gram-negative, anaerobic, and atypical bacteria (Summary of Product Characteristics [SmPC] and US Prescription Information [PI]).[4,5] In the US, tigecycline (Tygacil®) was approved by the US Food and Drug Administration (FDA) for complicated skin and skin-structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired bacterial pneumonia (CAP) for patients 18 years of age and older.[5] The European Medicines Agency (EMA)-approved SmPC states tigecycline is indicated in adults and children from the age of 8 years for treatment of cIAI and cSSTI, with the exception of diabetic foot infections (DFI).[4]

A mortality imbalance in adults has been demonstrated in meta-analyses of Phase 3 and Phase 4 active controlled tigecycline clinical trials in adults. This is reflected in tigecycline labels, and should be considered when contemplating paediatric use. Also, tigecycline is not generally recommended in patients <8 years because of potential effects on tooth development, a class effect of tetracyclines, although clearly the risk-benefit ratio needs to be considered when treating MDR infections. The product label indicates tigecycline should be avoided in patients <18 years-old unless no alternatives are available.[5] Proposed paediatric dosing recommendations have been developed through simulations

comparing therapeutic target attainment of twice daily doses ranging from 0.75–1.25 mg/kg. These simulations were based upon pharmacokinetic data from children,[6] and exposures in adults enrolled in Phase 2 and 3 trials.[7,8]

In the European Union (EU) the Paediatric Committee (PDCO) accepted limited tigecycline clinical data to support a paediatric indication (for children from the age of 8 years) based on the limited therapeutic options available, and the obvious unmet clinical needs. This resulted in a restricted paediatric indication for tigecycline to treat complicated skin and soft-tissue infections (cSSTI) and cIAI by the EMA only in situations in which other antibiotics are not suitable.

The restricted paediatric indication was based on the recent *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections*,[9] which provides approval guidelines for medications with limited paediatric clinical data for treatment of infections caused by MDR organisms for which there are few therapeutic options. Of note, *Mycobacterium* is not listed in the tigecycline European label. However, rapid-growing mycobacteria are included in *in vitro* activity in the US label. Clinical *Mycobacterium* infections treated with tigecycline are described.[10]

Although there are currently no plans for further paediatric clinical trials, it was recognised that therapeutic options to treat MDR infections in children are limited, and tigecycline is used off-label by clinicians. This report provides comprehensive information on tigecycline use in paediatrics, specifically with regard to available clinical data (including pharmacokinetics [PK] and safety information) and clinical use (real-world/outcomes data and reporting), both on-label and off-label.

METHODS

Available data were identified from published and unpublished sources including clinical trials, expanded access and compassionate use programs, healthcare record databases and patient safety monitoring. This information was summarized and presented here.

RESULTS

1. Pharmacokinetics

A Phase 1 ascending single dose study (Study P110) enrolled 24 children age 8–16 years (Table 1), recently recovered from infections. A single dose of tigecycline was administered to three dose groups: 0.5 mg/kg (maximum of 50 mg), 1 mg/kg (maximum of 100 mg), and 2 mg/kg (maximum of 150 mg) administered intravenously over 30 minutes. Sampling for pharmacokinetic analyses occurred before and at 0.5, 0.75, 1, 2, 4, 8, 12, 24, 36, and 48 hours after dose administration. As with adults, a distinctively two-compartment concentration-time curve was observed. The PK parameters were similar to those seen in adults, but with wider inter-subject variability. Renal clearance was low compared to total clearance (9.8%–39%).

A Phase 2 ascending multiple-dose study (Study 2207) in 58 children (age 8–11 years) included evaluation of steady-state PK parameters[6] (Table 1). Children with serious infections (cIAI, cSSSI, or CAP) received tigecycline 0.75, 1, or 1.25 mg/kg (maximum of 50 mg) every 12 hours (q12h) intravenously over 30 minutes. The PK parameters were consistent with those observed in the single-dose study and similar to adults with the exception of higher weight-normalised clearance in the younger children. Pharmacokinetic data from both paediatric studies were combined to develop a population PK model; only body weight was found to be a significant covariate of tigecycline plasma clearance (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000644/WC500191296.pdf).

2. Pharmacodynamics

In early development, the most informative pharmacokinetic/pharmacodynamic (PK/PD) efficacy parameter for tigecycline was the ratio of area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC) and was identified in a preclinical model as well as in adults with cSSSI and cIAI.[7,8,11] Therefore, assuming bacteria causing infections in children will respond similarly to tigecycline as in adults (i.e. assuming similar MICs for both patient groups), it is reasonable to expect similar efficacy in children administered a dose regimen that provides exposure (AUC) that matches the AUC in adults successfully treated. PK/PD simulations evaluated dosing regimens in children and used PK data from the studies in children, available data from adults who had participated in Phase 2 and 3 clinical trials, and microbiological data from the TEST (Tigecycline Evaluation Surveillance Trial, now part of the Antimicrobial Testing Leadership And Surveillance [ATLAS] program: https://atlas-surveillance.com) that was available at the time (2009). Regimens of 1.2 mg/kg (maximum dose 50 mg) q12h in children 8–11 years and 50 mg q12h in children 12–<18 years were predicted to achieve AUC and thus AUC/MIC values similar to adults receiving 50 mg q12h.

3. Clinical Data

Similar clinical efficacy has been observed between adults and children treated with tigecycline.

3.1 Study 2207

This study described above, was a Phase 2, open-label, multicentre study that enrolled 58 children with cSSTI, cIAI, and CAP.[6] Enrolment was permitted in only 1 dose cohort at a time and enrolment in the subsequent cohort was possible only after review of tolerability in the previous dose level. Overall, clinical cure rates at test-of-cure were 94.1% (16/17), 76.2% (16/21), and 75.0% (15/20) in the 0.75-, 1-, and 1.25-mg/kg cohorts, respectively (Table 1).

3.2 Compassionate Use Program

A compassionate use program was begun under the auspices of the sponsor's Clinical Research & Development Department. Available data were obtained from investigating physicians (who also provided narratives) and submitted to the sponsor for compilation and interpretation. In all, 104 adults and children from 15 countries were enrolled. The patient population included 92 adults, 10 with cystic fibrosis. Of the 12 children, 9 had cystic fibrosis (all with mycobacteria), 1 had vasculitis with mycobacteria, 1 had chronic myeloid leukaemia with *A. baumannii*, and 1 had a sternal wound with *A. baumannii* (Table 2).

In all paediatric cases (12/104), tigecycline was added after initial failure of other therapies and was used in combination with other agents including macrolides, cephalosporins, penicillins, beta-lactamase inhibitor combinations, aminoglycosides, carbapenems, doxycycline, colistin, and linezolid. The therapy duration varied and in some cases very prolonged. All 12 children survived; 7 achieved clinical improvement, 4 experienced treatment failure, and 1 patient had indeterminate response (unpublished data from the Compassionate Use Program) (Table 2). Clinical outcomes could not be attributed to tigecycline alone since numerous antibiotics were used prior to and concurrent with tigecycline.

Ten of the 12 children who had mycobacteria infection were included, in addition to adult patients from 2 other studies, in a report on the application of tigecycline-containing regimens for salvage treatment of rapidly-growing mycobacterial infections; however, no details on these children were described in this report.[10]

3.3 Other Published Reports

Zhu et al reported results from a retrospective chart review of 24 children hospitalized with primary or secondary infections and treated with tigecycline; pneumonia was the most common infection (71.4%).[12] The authors found 45.8% of patients had evidence of a response to tigecycline (clinical, microbiologic or both), primarily to infections caused by MDR bacteria. *A. baumannii* was the most commonly isolated pathogen and was confirmed in 50% of patients. Also, the 5 patients who experienced both clinical and microbiological responses were infected with *A. baumannii*. Six patients died because of infection (3) or their primary disease (3), e.g., congenital heart disease or hematologic malignancy. The authors noted the contribution of combinations of antibiotics and their synergistic mechanisms of action; tigecycline was most commonly combined with other antibiotics for Gram-negative bacteria. Tigecycline dosing used was considered effective and tolerable: an initial loading dose of 1.5 or 2 mg/kg followed by a maintenance dose of 1 mg/kg/dose q12h.

Similarly, Iosifidis et al reported a case series of 13 children (median age 8 years) with MDR infections (5 bacteraemias, 6 lower respiratory tract infections, and 3 other infections [sepsis, septic thrombophlebitis, and cSSTI]).[13] Pathogens were resistant to most or all antibiotics tested except tigecycline. A loading dose (1.8–6.5 mg/kg) was given (in all but 2 cases), followed by maintenance at 1–3.2 mg/kg q12h. No serious adverse events (AEs) were reported. Among tigecycline-treated patients receiving therapy for ≥5 days, clinical and microbiological improvement was seen in 7 of 11 (64%) and 4 of 7 (57%) patients, respectively; patients with bacteremia did not benefit from addition of tigecycline (3 out of 3 clinical failures and death). In contrast, among 8 non-bacteraemic patients who received tigecycline, clinical outcome improved in 7 patients (1 patient died) and only 1 experienced clinical failure and died.

4. Safety Data

In Study P110, no deaths occurred among the 25 children enrolled. Treatment-emergent AEs (TEAEs) occurred in approximately one-third of children and included headache (8%), nausea (12%), and vomiting (16%). One child had vomiting with associated dehydration, a serious AE (SAE) that resolved during hospitalisation. Another child withdrew because of a mild injection site reaction. All TEAEs were observed in other clinical studies of tigecycline (Table 1).

In Study 2207, no deaths occurred. TEAEs were reported in 44 (75.9%) children with nausea (28, 48.3%) and vomiting (27, 46.6%) being the most frequent. Compared with the 0.75 mg/kg group, significantly more children in the 1.25 mg/kg and 1 mg/kg group had nausea (60.0% and 61.9% vs 17.6%; P=0.018 and P=0.009, respectively) and more children had vomiting (55.0% and 52.4% vs 29.4%; difference was not significant). The majority of nausea and vomiting events were mild to moderate. Three (5.2%) children had SAEs, 1 with cIAI receiving 0.75 mg/kg of tigecycline, 1 with cSSSI receiving 1 mg/kg of tigecycline, and 1 with cSSSI receiving 1.25 mg/kg of tigecycline. Two (3.4%) discontinued tigecycline who were withdrawn because of AEs. In addition, children receiving 0.75 mg/kg of tigecycline defervesced, on average, 2 days later than those in the 1 or 1.25 mg/kg groups, suggesting a delayed response to therapy. No potentially clinically important laboratory results, vital signs, or electrocardiograms were identified as medically important. No new or unexpected safety concerns were observed with tigecycline (Table 1).

The Tigecycline Post-Authorization Safety Study (PASS) was an observational cohort study that employed retrospective chart abstraction study design in which pre-recorded patient-centred data were reviewed (EU registration number EUPAS3674).[14] The study enrolled 777 patients from 13 sites in 5 EU countries (2 sites in Austria, 4 in Germany, 3 in Italy, 2 in Greece, 2 in the UK). The study primary objectives were: 1) to evaluate the effectiveness of risk minimisation measures (RMM) for tigecycline by describing prescription patterns among patients treated with any dose of tigecycline for any

indication (on- or off-label) in the EU before and following implementation of RMM, and 2) to determine the incidence of superinfection and lack of efficacy among adult patients treated with approved doses of tigecycline for cIAI and cSSTI in the EU prior to and after implementation of RMM. Paediatric data are summarized in Table 3.

Although the number of children treated in the PASS is small, this study was conducted prior to approval of a restricted paediatric indication and further supports the need, albeit infrequent, for tigecycline use in children when other therapies are not suitable. This dataset is notable mostly for: 1) small numbers of children, and 2) the types of infections for which tigecycline was used. Although not explicitly stated, the children who received tigecycline might have received it because other therapies failed and/or *in vitro* activity indicated tigecycline was the only agent with activity.

The Pfizer Global Safety Database collects information from a wide range of sources including patient and healthcare professional reports to Pfizer, clinical trials and safety cases reported in the literature. In 2014, there were 82 paediatric cases (149 events). The mean age was 10.2 years. The most frequently reported AEs were off-label use, vomiting, and nausea; all other recorded events occurred in <5% of patients (Table 4). In these patients, tigecycline was used most frequently for Gram-negative and mycobacterial infections (Table 5). In cases where dosage information was available, the majority ranged from 25–50 mg q12h, consistent with known PK data and proposed dosing in children.

5. Ongoing Pharmacovigilance

In addition to the Pfizer Global Safety Database, other sources of data regarding tigecycline use in children include US FDA MedWatch reporting and healthcare or insurance databases on patient outcomes. Limited paediatric data on tigecycline use can be obtained from sources such as Premier

(www.premierinc.com/), Arlington Medical Resources (AMR, www.amr-data.com), and the Pediatric Health Information system (PHIS, www.childrenshospitals.org/).

DISCUSSION

This report summarizes data from a wide range of sources to provide a comprehensive description of paediatric tigecycline use. It describes tigecycline as a treatment for children with serious MDR infections and limited therapeutic options. These data sets have strengths and weaknesses. The data available offer important insights into dosing, PK, tolerability, and AE profiles but lack the breadth of information provided by Phase 3 clinical trials. Large healthcare databases include greater patient numbers with diverse geographic representation but are limited in depth of data and outcomes reporting. Published cases offer detailed patient history and response to treatment but are not randomised and controlled.

Clinical trials conducted in adults used loading doses to achieve therapeutic concentrations quickly. However, clinical studies confirmed AUC was most closely related to efficacy,[7,8] and multiple- versus single-dose PK data in adults suggested that the steady state accumulation was less than that predicted. Thus a loading dose may not be needed. In an effort to improve tolerability, the paediatric Phase 2 study conducted by Purdy et al did not include a loading dose.[6]

The need for effective treatments against resistant infections in children, is indicated by the TEST data collection of paediatric isolates and the clinical use of tigecycline in the Compassionate Use Study, PASS, the Pfizer Safety Database, and case reports, and is supported by data from AMR, Premier and PHIS. However, there is no standard method of conducting antibiotic pharmacovigilance, particularly for off label use and treatment of MDR infections.

Consideration of tigecycline's pharmacokinetic characteristics may assist clinicians in dosing. Taking into account not only physical but physiological differences between children and adults in drug absorption, distribution, metabolism, and elimination is important.[15] The volume of distribution of tigecycline is very large and so differences in body composition in very young children are unlikely to significantly affect drug concentrations. Immaturity of the cytochrome P450 enzymes observed in very young infants would not be expected to alter tigecycline PK as it is not metabolized, but eliminated unchanged in bile, nor would the low glomerular filtration rate and immaturity of tubular excretion, because of the very modest excretion in urine.

More data are needed in children but regulatory and logistical challenges remain. The Phase 1 and Phase 2 Pfizer clinical trials excluded any child under age 8 years. This exclusion was necessary due to known tetracycline effects discussed above, and these effects, along with the adult mortality imbalance, preclude further clinical trials in children below age 8. The PASS study also had no child under age 8 years. Only the compassionate use trial had a single child enrolled under age 8 (age 3 years). In view of this lack of clinical data below age 8, the current label language should be followed, and use below age 8 should be at the discretion of the physician when no other alternative is available, and when the benefits are determined to outweigh the risks. A recent systematic review revealed an urgent need for improved harmonization between EMA and FDA on design and conduct of paediatric antibiotics trials.[16] However further clarity may be forthcoming. For instance, as of 2017, the EMA is developing a draft addendum to the guideline on evaluation of medicinal products indicated for treatment of paediatric bacterial infections (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/04/WC500205026.pdf). Collaboration between pharmaceutical companies and paediatric academic specialty networks (as

has occurred with paediatric antiretroviral drug registries) should be explored in the setting of antibiotic treatment of serious MDR infections.

CONCLUSIONS

Information presented here may help guide the appropriate use of tigecycline in children with MDR infections. Continued pharmacovigilance from real-world observational studies may also further refine appropriate use of tigecycline in this population. The manufacturer and academic collaborators chose to summarise these data to help advance understanding of tigecycline use in paediatrics, a topic that has attracted much investigation.[17] We encourage other companies to undertake similar exercises in situations where studies cannot be conducted, particularly for specific patient populations such as neonates and children.

ACKNOWLEDGEMENTS

This study was funded by Pfizer. Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data

access agreement with Pfizer. Editorial support was provided by Thomas Gegeny of Engage Scientific Solutions and was funded by Pfizer.

DISCLOSURE

MS received no funding from Pfizer for this work. KAR received no funding from Pfizer for this work. HT, NB-P, MT, AH, SR, JK-B, HD-P, and MW are Pfizer employees.

REFERENCES

1. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet*. 2015;385:430-440.
2. Laxminarayan R, Bhutta ZA. Antimicrobial resistance-a threat to neonate survival. *Lancet Glob Health*. 2016;4:e676-677.
3. Davies JC, Rubin BK. Emerging and unusual gram-negative infections in cystic fibrosis. *Semin Respir Crit Care Med*. 2007;28:312-321.
4. Tygacil® SmPC. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000644/WC500044508.pdf Accessed 19 July, 2018.
5. Tygacil® PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205645s001lbl.pdf Accessed 19 July, 2018.

6. Purdy J, Jouve S, Yan JL, et al. Pharmacokinetics and safety profile of tigecycline in children aged 8 to 11 years with selected serious infections: a multicenter, open-label, ascending-dose study. *Clin Ther*. 2012;34:496-507 e491.
7. Meagher AK, Passarell JA, Cirincione BB, et al. Exposure-response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. *Antimicrob Agents Chemother*. 2007;51:1939-1945.
8. Passarell JA, Meagher AK, Liolios K, et al. Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. *Antimicrob Agents Chemother*. 2008;52:204-210.
9. European Medicines Agency. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500153953.pdf. Accessed 19 July, 2018.
10. Wallace RJ, Jr., Dukart G, Brown-Elliott BA, et al. Clinical experience in 52 patients with tigecycline-containing regimens for salvage treatment of Mycobacterium abscessus and Mycobacterium chelonae infections. *J Antimicrob Chemother*. 2014;69:1945-1953.
11. van Ogtrop ML, Andes D, Stamstad TJ, et al. In vivo pharmacodynamic activities of two glycylcyclines (GAR-936 and WAY 152,288) against various gram-positive and gram-negative bacteria. *Antimicrob Agents Chemother*. 2000;44:943-949.
12. Zhu ZY, Yang JF, Ni YH, et al. Retrospective analysis of tigecycline shows that it may be an option for children with severe infections. *Acta Paediatr*. 2016;105:e480-484.

13. Iosifidis E, Violaki A, Michalopoulou E, et al. Use of Tigecycline in Pediatric Patients With Infections Predominantly Due to Extensively Drug-Resistant Gram-Negative Bacteria. *J Pediatric Infect Dis Soc*. 2016.
14. Frajzyngier V, Quintana A, Tucker H, et al. An Evaluation of the Effectiveness of Risk Minimization Measures for Tigecycline in the European Union. *Pharm Med*. 2017;31:89-99.
15. Bouzom F, Walther B. Pharmacokinetic predictions in children by using the physiologically based pharmacokinetic modelling. *Fundam Clin Pharmacol*. 2008;22:579-587.
16. Folgori L, Bielicki J, Ruiz B, et al. Harmonisation in study design and outcomes in paediatric antibiotic clinical trials: a systematic review. *Lancet Infect Dis*. 2016;16:e178-189.
17. Mastrolia MV, Galli L, De Martino M, et al. Use of tigecycline in pediatric clinical practice. *Expert Rev Anti Infect Ther*. 2017;15:605-612.

Table 1. Key clinical trial data on tigecycline use in children

Study number	**3074A1-110-US (Study P110)**	**3074K4-2207-WW (Study 2207)[6] (NCT-00488345)**
Design and description	• Open-label, SAD, sequential study in 2 age groups (8–11 years and 12–16 years) • Sampling for PK analyses before and at 0.5, 0.75, 1, 2, 4, 8, 12, 24, 36, and 48 hours after dose administration	• Open-label, multicentre, Phase 2, MAD study to assess PK, safety and tolerability in children with serious infections • Assessments included: (1) daily VS; (2) blood samples day 3 for PK, 12-lead ECG, and blood/serum tests; (3) clinical evaluation on day 14 or last day of treatment, physical and lab assessments; (4) TOC evaluation between day 10 and 21 days after last dose, evaluation of clinical response (cure, failure, indeterminate), VS, etc. • Sampling for PK before first dose, before and immediately after a dose on or after day 3 as well as 2, 6, and 12 hours after start of infusion
N	24	58 (47 with PK data)
Population	Age 8–16 years	Age 8–11 years with CAP, cIAI, or cSSSI
Dosing	0.5, 1, and 2 mg/kg IV up to a maximum dose of 50 mg (0.5 mg/kg dosing), 100 mg (1 mg/kg dosing), or 150 mg (2 mg/kg dosing)	0.75, 1, or 1.25 mg/kg (up to a maximum dose of 50 mg) every 12 hours infused over ~30 min
Primary outcome(s)	To assess PK of SAD	To assess PK properties and tolerability
Secondary outcome(s)	Safety and tolerability of single doses	To assess (descriptively) the efficacy

	administered (IV)	
Key results (PK, Efficacy, etc.)	• PK parameters were similar to adults, but with higher variability. As with adults, initial high concentrations followed by rapid distribution and slower elimination • Renal clearance was low compared to total clearance (9.8% to 39%)	• Based on weight, BSA, or BMI versus clearance, smaller children had lower clearance than larger children • PD simulations using PK data from this study, data from adult studies, and TEST micro-biological data showed 1.2 mg/kg every 12 h (maximum 50 mg) achieved AUC/MIC ratios observed in adults receiving 50 mg every 12 h • Tigecycline C_{max} or $AUC_{0–24h}$ was not found to contribute to occurrence of nausea or vomiting (logistic regression analyses) • Overall clinical cure rates at the TOC were 94.1% (16/17), 76.2% (16/21), and 75.0% (15/20) in the 0.75-, 1-, and 1.25-mg/kg cohorts, respectively
Safety	• No deaths occurred, and TEAEs occurred in approximately one third of patients • TEAEs included headache (8%), nausea (12%), and vomiting (16%). Nausea and vomiting occurred at the higher doses of 1 and 2 mg/kg and were considered possibly related to tigecycline	• 46 patients (79.3%) experienced 1 or more AEs, with no significant differences between the dosage groups • Most AEs were GI related • Most frequent AE was nausea, in 29/58 patients. Prevalence of nausea was significantly higher (>60%) in the 1.25- and 1.0-mg/kg groups than in the 0.75-mg/kg group (18%); $P<0.01$ • 3 patients experienced SAEs (post-operation wound infection, anal fistula, and abdominal pain), all of which resolved by end of study

AE, adverse event; AUC, area under curve; BMI, body mass index; BSA, body surface area; CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infection; cSSSI, complicated skin and skin structure infection; ECG, electrocardiography; GI, gastrointestinal; IV, intravenous; MAD, multiple ascending dose; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; SAD, single ascending dose; SAE, serious adverse event; TEAE, treatment emergent adverse events; TEST, the Tigecycline Evaluation and Surveillance Trial; TOC, test-of-cure; VS, vital signs.

Table 2. Paediatric outcomes in Compassionate Use Study of Tigecycline

Age / Sex / Location	**Indication (Isolate)**	**DOSE (mg) weight if given**	**Length of treatment**	**Outcome**
12, F, USA*	CF, *Mycobacterium. abscessus*	25 mg BID; also 36 mg QD at one point	13 months	Improved
12, F, Israel*	CF, *M. abscessus*	30 mg to 25 mg BID; 30 kg weight	9 months	Improved
12, M, USA*	CF, *M. abscessus*	25-35 mg Q12h	>26 months	Improved
17, F, Israel*	CF, *M. abscessus*	50 mg BID	4 months	Failure
17, F, UK	CF, *M. abscessus*	Unknown	Unknown	Indeterminate
12, F, Israel*	CF, *M. abscessus*	30 mg QD to 40 mg QD to 25 mg Q12h	3 months	Failure
16, M, UK	CF, *M. abscessus*	100 mg QD	5 months	Improved
12, F, UK	CF, *M. chelonae*	unknown	1.5 months	Failure
13, F, UK	CF, *M. abscessus*	50 BID to 40 BID discontinued due to nausea/vomiting; 40 kg	1 month	Failure
13, F, USA	Vasculitis, *M. chelonae*	0.5mg/kg BID	2 months	Improved
3, M, Israel	CML, *Acinetobacter baumannii*	40x2, 20x2, then 0.5mg/kg	>1 month	Improved
17, M, Australia	Sternal osteomyelitis *A. baumannii*	50 Q12	2 months	Improved

In all of these cases, tigecycline was added after initial failure of other therapies and was used in combination with other agents.

*These patients are also listed in the Pfizer Safety Database.

Table 3. Paediatric patient data from the Tigecycline Post-Authorization Safety Study (PASS)

Patient	Age, years	Loading dose	Maintenance dose (q12h)	Duration of Use, days	Ward of admission	Indication
1	14	100 mg	50 mg	14	ICU	Intestinal perforation with abscess or faecal contamination
2	15	100 mg	>50 mg	13	Surgical	Wound infection
3	17	100 mg	50 mg	14	ICU	Bacteraemia
4	12	<100 mg	50 mg	31	Medical	Cystic fibrosis with *Pseudomonas* and *Stenotrophomonas* colonisation
5	16	No loading dose	50 mg	22	Other	Exacerbation of cystic fibrosis (pulmonary)
6	14	100 mg	50 mg	12	Other	Bronchiectasis-infective exacerbation
7	14	100 mg	Unknown	7	Other	Chronic *Mycobacterium abscessus* infection

Table 4. Adverse events recorded in ≥2% of paediatric patients in the Tigecycline Global Safety Database (N=82)

Adverse event	**Frequency (%)**
Off label use*	23.2
Vomiting	14.6
Nausea	12.2
Condition aggravated	4.9
Sepsis	4.9
Other adverse events with the same frequency	
Acute respiratory failure, cystic fibrosis, drug ineffective, pancreatitis, pancreatitis acute, and transaminases increased	3.7
Abdominal pain, alanine transaminase increased, blood fibrinogen decreased, circumstance capable of leading to medication error, death, expired drug administered, hyperbilirubinaemia, hypertension, muscle spasms, neutropenia	2.4

*"Off label use" has been recorded as an adverse event in the Tigecycline Global Safety Database that uses MedDRA preferred terms.

Table 5. Breakdown of types of infection reported in Global Safety Database for Tigecycline

	Global cases
Paediatric use of tigecycline (N)	82
Cystic fibrosis diagnosis	21
Pathogen Reported	38*
Mycobacteria	13
Mycobacterium abscessus	9
Cystic fibrosis diagnosis	9
Other bacteria	27†
Acinetobacter	6
Stenotrophomonas	5
Klebsiella	4
Escherichia coli	5

*Two of the "Other bacteria" cases had a *Mycobacterium* isolated as well. Thus there were only 38 cases in which there was a "Pathogen reported".

†Some of the cases listed under "Other bacteria" had multiple isolates in a single case; not all of the isolated "Other bacteria" are listed in Table 5.