Allergan (Research Grant or Support)Allergan (Research Grant or Support)Amplyx Pharmaceuticals (Research Grant or Support)Cidara Therapeutics (Research Grant or Support)Cidara Therapeutics (Research Grant or Support)Cipla Ltd. (Research Grant or Support)Cipla Ltd. (Research Grant or Support)Fox Chase Chemical Diversity Center (Research Grant or Support)GlaxoSmithKline (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Merck (Research Grant or Support)Merck (Research Grant or Support)Merck & Co, Inc. (Research Grant or Support)Merck & Co, Inc. (Research Grant or Support)Paratek Pharma, LLC (Research Grant or Support)Pfizer (Research Grant or Support)Qpex Biopharma (Research Grant or Support) Jill Lindley, Allergan (Research Grant or Support)Qpex Biopharma (Research Grant or Support) Timothy B. Doyle, Allergan (Research Grant or Support)Allergan (Research Grant or Support)Cipla Ltd. (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Pfizer (Research Grant or Support)Qpex Biopharma (Research Grant or Support) Olga Lomovskaya, PhD, Qpex Biopharma (Employee)

167. A Phase 1b, Randomized, Double-blind, Placebo-controlled, Multiple-ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of DSTA4637S in Patients with *staphylococcus Aureus* Bacteremia Receiving Standard-of-care Antibiotics

Jeremy Lim, PharmD[1]; Nicholas Lewin-Koh, PhD[1]; Tom Chu, MD, PhD[2]; Sharon M. Rymut, PhD[3]; Aklile Berhanu, PhD[1]; Montserrat Carrasco-Triguero, PhD[4]; Carrie C. Rosenberger, PhD[1]; Wouter L. Hazenbos, PhD[5]; Loren G. Miller, MD, MPH[6]; Vance G. Fowler, Jr., MD, MHS[7]; Jose M Miro, MD PhD[8]; Jessica A. Couch, PhD[1]; Melicent C. Peck, MD, PhD[3]; [1]Genentech, Inc., South San Francisco, California; [2]Genetech, Inc., South San Francisco, California; [3]Genentech, San Francisco, California; [4]Genentech - South San Francisco - CA, South San Francisco, California; [5]1 DNA Way, Genentech, South San Francisco, South San Francisco, California; [6]Harbor UCLA, Torrance, California; [7]Duke University, Durham, North Carolina; [8]Hospital Clinic of Barelona, Barcelona, Catalonia, Spain

Session: O-32. Novel agents

Background: New treatment approaches for complicated *Staphylococcus aureus* bacteremia (SAB) are needed. DSTA4637S is a THIOMAB^{TM} antibody-antibiotic conjugate consisting of an engineered human IgG1 monoclonal antibody that binds to wall teichoic acid at the surface of *S. aureus*, a protease-cleavable linker, and a novel rifamycin class antibiotic, dmDNA31. This Phase 1b study assessed the safety, tolerability, and pharmacokinetics of DSTA4637S in patients with complicated SAB.

Methods: Multicenter, double-blind, placebo controlled, multiple-ascending dose clinical trial. Patients 18–79 years old with complicated SAB requiring at least 4 weeks of IV anti-staphylococcal standard-of-care (SOC) antibiotics were randomized to receive 4–6 doses of 15, 45, and 100 mg/kg IV DSTA4637S or placebo (6 active:2 placebo) every 7 days in combination with SOC antibiotics. Patients needed ≥ 1 blood culture positive for *S. aureus* collected within 120 hours prior to randomization. Patients were followed for 120 days after the end of treatment.

Results: Twenty-five patients with complicated SAB (bone & joint, n=14; endocarditis, n=5; other endovascular, n=5; pneumonia, n=1) were randomized and received 1–6 doses of study drug (19 active:6 placebo). Nine patients (36%) had MRSA. Ten patients completed ≥4 doses of DSTA4637S. The most common treatment-related adverse events were infusion-related reactions (IRRs) (5/19), and abnormal serum color (5/19)/skin discoloration (3/19 (due to dmDNA31). IRRs were not dose-dependent and were reversible with supportive care. Ten of 19 patients (40%) discontinued study drug (9 DSTA4637S,1 placebo); 4/19 (21%) due to IRR. DSTA4637S recipients showed no dose-related changes in laboratory values or vital signs vs. placebo. Observed exposures (C_{max} and AUC) were lower in patients immediately after dosing compared to a prior study in healthy volunteers; minimal accumulation occurred. No obvious trends in exploratory bacterial and inflammatory biomarkers were observed between treatment groups.

Conclusion: DSTA4637S in patients with complicated SAB demonstrated increased IRRs and decreased exposure compared to healthy volunteers, highlighting the importance of Phase I studies of novel treatments in infected SAB patients and not simply healthy controls.

Disclosures: Jeremy Lim, PharmD, Roche (Employee, Shareholder) Nicholas Lewin-Koh, PhD, Genentech (Employee) Tom Chu, MD, PhD, Genentech (Employee) Sharon M. Rymut, PhD, Genentech (Employee, Shareholder) Aklile Berhanu, PhD, Genentech, Inc. (Employee, Equity interest (Stock/Stock Options)) Montserrat Carrasco-Triguero, PhD, Genentech (Employee) Carrie C. Rosenberger, PhD, Genentech (Employee, Shareholder) Wouter L. Hazenbos, PhD, Genentech (Employee) Loren G. Miller, MD, MPH, genentech (Grant/Research Support) Vance G. Fowler, Jr., MD, MHS, Achaogen (Consultant)Actavis (Grant/Research Support)Advanced Liquid Logics (Grant/Research Support)Affinergy (Consultant, Research Grant or Support)Affinium (Consultant)Allergan (Grant/Research Support) Ampliphi Biosciences (Consultant)Basilea (Consultant, Research Grant or Support) Bayer (Consultant)C3J (Consultant)Cerexa (Consultant, Research Grant or Support) Contrafect (Consultant, Research Grant or Support)Cubist (Grant/Research Support) Debiopharm (Consultant)Destiny (Consultant)Durata (Consultant)Forest (Grant/Research Support)Genentech (Consultant, Research Grant or Support)Integrated Biotherapeutics (Consultant)Janssen (Consultant, Research Grant or Support)Karius (Grant/Research Support)Locus (Grant/Research Support)Medical Biosurfaces (Grant/Research Support)Medicines Co. (Consultant)Medimmune (Consultant, Research Grant or Support)Merck (Consultant, Research Grant or Support)NIH (Grant/Research Support)Novadigm (Consultant)Novartis (Consultant, Research Grant or Support)Pfizer (Grant/Research Support)Regeneron (Consultant, Research Grant or Support)Tetraphase (Consultant)Theravance (Consultant, Research Grant or Support)Trius (Consultant)xBiotech (Consultant) Jose M Miro, MD PhD, GENENTECH (Consultant, Scientific Research Study Investigator, Advisor or Review Panel member) Jessica A. Couch, PhD, Genentech (Employee, Shareholder) Melicent C. Peck, MD, PhD, Genentech (Employee)

168. Efficacy of the Novel gwt1 Inhibitor APX2039 in a Rabbit Model of *cryptococcus Meningitis*

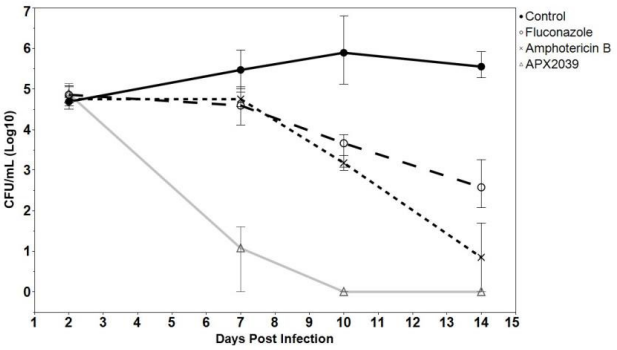
Karen J. Shaw, PhD[1]; Charles D. Giamberardino, Jr., MR[2]; Quinlyn A. Soltow, PhD[1]; Jennifer Tenor, PhD[2]; Dena Toffaletti, PhD[2]; Jane-Valeriane Boua, BS[2]; Choiselle Marius, n/a[2]; Julia R. Palmucci, n/a[2]; John R. Perfect, MD[2]; [1]Amplyx Pharmaceuticals, San Diego, California; [2]Duke University, Durham, North Carolina

Session: O-32. Novel agents

Background: Cryptococcal meningitis (CM), caused primarily by *Cryptococcus neoformans*, is uniformly fatal if not treated. Treatment options are limited especially in resource-poor geographical regions, and mortality rates remain high despite current therapies. New oral treatment options are needed that demonstrate rapid reductions in CFU in CSF and brain tissue.

APX2039 is a novel inhibitor of the fungal Gwt1 enzyme, which catalyzes an early step in glycosylphosphatidyl inositol (GPI) anchor biosynthesis. It is highly active against both *C. neoformans* and *C. gattii* and has previously demonstrated significant efficacy in a mouse delayed-treatment model of CM.

CSF Fungal Burden in Rabbits



Methods: Male New Zealand White rabbits were inoculated with *C. neoformans* H99 (1.4×10^6 CFU) directly into the cisterna magna. Rabbits were immunosuppressed with cortisone acetate at 7.5 mg/kg (i.m.), starting on Day -1 relative to inoculation and then administered drug daily throughout the 14-day experimental period. Treatment was initiated on Day 2 postinfection and continued through Day 14 consisting of: 50 mg/kg APX2039 PO (BID), 80 mg/kg fluconazole (FLU) PO (QD), c) 1 mg/kg amphotericin B deoxycholate (AMB) IV (QD); and vehicle control. CSF was removed via an intracisternal tap on Days 2, 7, 10 and 14 post-infection and CFU/ml was assessed. Animals were sacrificed on Day 14 and CFU/g brain tissue was assessed.

Results: APX2039 demonstrated rapid reduction in CFU in both CSF and brain tissue. The range in CFU values in rabbit CSF is shown (Figure). Reductions in CFU were statistically different from the control group for all treatment groups. APX2039 was also different from both FLU and AMB and resulted in sterilization in CSF by Day 10. Brain harvested on Day 14 demonstrated a reduction in CFU/g tissue vs control of 1.8 $\log_{10}$ and 3.4 $\log_{10}$ for FLU and AMB, respectively, while a > 6 $\log_{10}$ reduction (tissue sterilization) was observed for APX2039.

Conclusion: APX2039 demonstrated potent efficacy in a rabbit model of CM. The more rapid clearance in CSF than either AMB or FLU, as well as > 6 $\log_{10}$ reduction in brain CFU highlights the unique properties of this drug, warranting further investigation of this molecule for the treatment of CM.

Disclosures: **Karen J. Shaw, PhD**, **Amplyx** (Consultant)**Forge Therapeutics** (Consultant) **Charles D. Giamberardino, Jr., MR**, **Box** (Shareholder) **John R. Perfect, MD**, **amplyx** (Grant/Research Support)**astellas** (Grant/Research Support)**astellas** (Grant/Research Support)

169. AT-752, an Oral Guanosine Nucleotide Prodrug, Exhibits Potent *in Vitro* Activity Against Flaviviruses and Prevents Disease Progression in a Dengue Mouse Model

Steven S. Good, MS[1]; Adel Moussa, PhD[1]; Xiao-Jian Zhou, PhD[1]; Jean-Pierre Sommadossi, PhD[1]; Keith Pietropaolo, BA[1]; [1]Atea Pharmaceuticals, Inc., Boston, Massachusetts

Session: O-32. Novel agents

Background: The increasing global prevalence of human Dengue virus infection and the potential for life-threatening sequelae highlight the significance of this unmet medical need. Here we report the potent *in vitro* activity of AT-281, the free base form of AT-752, against Dengue virus and other flaviviruses and the *in vivo* efficacy of AT-752 in a mouse model of Dengue viral disease.

Methods: Antiviral activities of serial dilutions of AT-281 were evaluated in infected Huh-7 cells. Effective concentrations of AT-281 required to inhibit virus yield reduction by 90% (EC_{90}) and to prevent cytopathic effect by 50% (EC_{50}) were

determined, respectively, by visual examination and by neutral red staining, as was cytotoxicity. AG129 (α-, β- and γ-interferon knock-out) mice received an oral dose of AT-752 (1000 mg/kg) 4 h before s.c. inoculation with Dengue virus type 2 (strain D2Y98P, 1x10^5 virus particles) followed by b.i.d. doses (500 mg/kg) for 7 days starting 1 h post-inoculation (p.i.). Six groups each (n=5) of treated and control mice were scheduled to be sacrificed on days 4, 6, 7, 8, 10 and 21 p.i. with serum and spleen viral RNA levels determined by plaque assay. AT-281 efficacy was evaluated based on overall health score, survival, weight loss and viral load in serum and spleen.

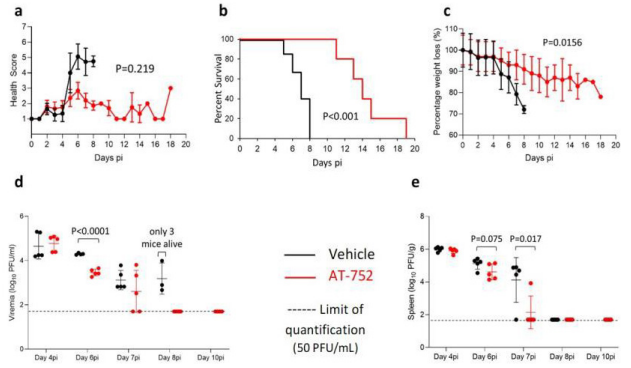
Results: *In vitro* EC_{90} values for AT-281 against Dengue, West Nile and Yellow Fever viruses ranged from 0.26 to 0.64 μM and EC_{50} values for Zika and Japanese encephalitis were 0.21 and 0.64 μM, respectively (Table 1). No toxicity was observed up to the highest concentrations tested (172 μM). Oral administration of AT-752 to Dengue-infected AG129 mice substantially improved survival, prevented weight loss and lowered viral loads by day 6, with virus being undetectable on day 8 and thereafter (Figure 1). Serum and spleen viral loads in control mice declined between days 4 and 8 but no control mice survived beyond day 8. In contrast, AT-752 treated mice survived up to day 19, eventually succumbing to model-induced CNS sequelae.

Table 1. Antiviral Activity of AT-281 Against Various Flaviviruses in Huh-7 Cell Cultures

Virus	Strain	EC_{90} (μM)	CC_{50} (μM)	SI[a]
Dengue type 2	New Guinea C	0.64	>172	>270
Japanese encephalitis	SA-14	0.21[b]	>172	>820
West Nile	Kern 515, WNo2	0.43	>172	>400
Yellow Fever	YFV 17D	0.26	>172	>660
Zika	MR766	0.64[b]	>172	>270

[a]SI = selectivity index (CC_{50}/EC_{90} or CC_{50}/EC_{50})
[b]EC_{50}

Figure 1. Efficacy of AT-752 in the AG129 mouse model of Dengue infection. Panel a: health score: 1, healthy; 2, coat slightly ruffled; 3, coat ruffled/wet; 4, coat very ruffled, eyes slightly closed/inset; 5, coat very ruffled, eyes closed/inset; 6, coat very ruffled, eyes closed/inset, moribund requiring humane euthanasia; 7, found dead. Panel b: Kaplan-Meier survival plot. Panel c: percent weight loss. Panel d: serum viremia. Panel e: spleen viral load.



Conclusion: The potent activity of AT-281 against Dengue virus *in vitro* and the efficacy of its salt form, AT-752, in the terminal AG129 mouse model warrant further clinical development of the drug. Preclinical safety studies are in progress and clinical trials will be initiated thereafter.

Disclosures: Steven S. Good, MS, Atea Pharmaceuticals, Inc. (Employee) Adel Moussa, PhD, Atea Pharmaceuticals, Inc. (Employee) Xiao-Jian Zhou, PhD, Atea Pharmaceuticals, Inc. (Employee) Jean-Pierre Sommadossi, PhD, Atea Pharmaceuticals, Inc. (Board Member) Keith Pietropaolo, BA, Atea Pharmaceuticals, Inc. (Employee)

170. Acute Flaccid Myelitis: Patient Characteristics and Prospective Follow-up Study at Children's National Hospital, 2013–2019

Alexandra B. Yonts, MD[1]; Nada Harik, MD[2]; Alyssa Doslea, MS[1]; Jonathan Murnick, MD, PhD[1]; Jessica Carpenter, MD[1]; Elizabeth Wells, MD[1]; Roberta L. DeBiasi, MD, MS[3]; [1]Children's National Hospital, Silver Spring, Maryland; [2]Children's National Health System, Washington, District of Columbia; [3]Children's National Health System/ George Washington Univ School of Medicine, Washington, District of Columbia

Session: O-33. Pediatric Infections and Immunology

Background: Acute Flaccid Myelitis (AFM), diagnosed almost exclusively in children, is characterized by sudden onset flaccid weakness in one or more extremities with distinct gray matter spinal cord lesions on magnetic resonance imaging (MRI), with or without cerebrospinal fluid (CSF) pleocytosis. Outbreaks of AFM have occurred biennially since 2014. Although the definitive causative agent(s) remain unknown, current data support an association with Enteroviruses D68 and A71. Treatment is supportive and long-term prognosis is variable, with many children having persistent motor deficits.

Methods: In this prospective cohort study, we identified patients with clinical and radiographic presentation consistent with AFM at Children's National Hospital (CNH) from 2013–2019. Medical records and MRIs of identified patients were then reviewed by members of the multidisciplinary CNH AFM Task Force to identify those meeting diagnostic criteria for AFM. Identified patients had follow-up arranged in the multidisciplinary AFM clinic for exam, functional motor assessment and quality of life questionnaires (Peds QL, PROMIS and NeuroQoL).

Results: Since 2013, we identified 22 patients meeting criteria for AFM at CNH. The average age of our patients was 7.25 years (range 6 months to 16 years); almost 2/3 of patients had CSF pleocytosis. Half of patients presented with initial neurologic complaint of single limb weakness. Other presenting neurological symptoms included ataxia, bilateral lower extremity weakness and ophthalmoplegia. A potential infectious cause was identified in the CSF, blood, nasopharynx or stool of 9 patients. As of November 2019, 7 of 21 patients have had follow-up evaluation; 1 had no improvement, 4 had partial improvement but with persistent motor deficits, and 2 had complete resolution. Two patients/families have completed quality of life questionnaires to date.

CNH AFM Patient Characteristics and Results

Total # patients	**22**
Male Gender	**17 (77%)**
Average age	**7.25 years (6 mo-16 yrs)**
Average CSF WBC Count	**118**
Pathogens identified (n= 9/22) B=blood, S= stool, R= NP respiratory swab	-Parvovirus (B) -Parechovirus (S) -Enterovirus A71 (S) -Coronavirus (R) -West Nile Virus (B) -Rhino/Entero (R) x 2 -Coxsackie B (B) -Borrelia burgdorferi (B)
Follow-Up Neurological Symptoms Status (n=7/22)	- Complete resolution: 2 - Improved: 4 - No change: 1 - Worse: 0 - Died: 1

Conclusion: Similar to other centers, the majority of CNH AFM patients with follow-up to date have persistent and significant long term motor deficits. Assessment of quality of life is an important aspect that has not yet been formally assessed in other studies and will provide useful information regarding the experience of these patients and help identify goals for optimizing care in the future.

Disclosures: **All Authors**: No reported disclosures

171. Short-course Antimicrobial Therapy for Paediatric Respiratory Infections (SAFER): a multicentre, Randomized, Controlled, Blinded, Noninferiority Trial

Jeffrey Pernica, MD, MSc, FRCPC, DTMH[1]; Stuart Harman, MD, FRCPC[2]; April J. Kam, MD MScPH FRCPC[3]; Redjana Carciumaru, MSc[3]; Thuva Vanniyasingam, PhD[4]; Tyrus Crawford, B.Soc.Sc.[5]; Dale Dalgleish, RN, BHScN, RN, BHScN[6]; Sarah Khan, MD, MSc, FRCPC[7]; Martha Fulford, MD FRCPC[3]; Cheryl L. Main, MD, FRCPC[8]; Robert Slinger, MD[9]; Marek Smieja, MD PhD FRCPC[3]; Lehana Thabane, PhD[3]; Mark Loeb, FRCPC, MD[10]; [1]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada; [2]University of Ottawa, Ottawa, Ontario, Canada; [3]McMaster University, Hamilton, Ontario, Canada; [4]The Research Institute of St Joe's Hamilton, Hamilton, Ontario, Canada; [5]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada; [6]CHEO, Manotick, Ontario, Canada; [7]McMaster University, Hamilton, Ontario, Canada, Hamilton, Ontario, Canada; [8]Hamilton Health Sciences and Hamilton Regional Laboratory Medicine Program, Hamilton, Ontario, Canada; [9]Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; [10]McMaster University, Hamilton, ON, Hamilton, Ontario, Canada

Session: O-33. Pediatric Infections and Immunology

Background: Community-acquired pneumonia (CAP) is a common occurrence in childhood; consequently, evidence-based recommendations for its treatment are required. The study objective was to determine if, in previously healthy children presenting to the emergency department (ED), 5 days of high-dose amoxicillin led to noninferior rates of clinical cure at 14–21 days post-enrolment compared with 10 days of high-dose amoxicillin.

Methods: The SAFER study was a multicentre, randomized, parallel-group, multiple-blinded, controlled, noninferiority study, enrolling between 2012–2014 (single centre pilot) and then 2016–2019 (follow-up main study). Children aged 6 months – 10 years with all of the following were eligible: fever within 48h; a respiratory symptom/sign; a chest radiograph consistent with pneumonia as per the emergency MD; and a primary diagnosis of CAP. Children were excluded if they required hospitalization, had any medical comorbidities, or if they were already receiving beta-lactam antibiotic therapy. The intervention of interest was 5 days of high-dose amoxicillin followed by 5 days placebo. The control (standard care) arm received 5 days of high-dose amoxicillin followed by a different formulation of 5 days of high-dose amoxicillin. The primary outcome was clinical cure at 14–21 days post-enrolment. The pre-set noninferiority margin was 0.075 less than the clinical cure risk difference (1-sided 97.5% CI).

Results: Of the 281 participants, 119 (42%) were female; the median age was 2.6 y (25–75%ile 1.6–4.9 y). There were 140 randomized to short-course treatment and