Clinical Pharmacology Perspectives on the Antiviral Activity of Azithromycin and Use in COVID-19

Bharat Damle[1]; Manoli Vourvahis[1]; Erjian Wang[2];

Joanne Leaney[3]; and Brian Corrigan[4]

[1] Pfizer Global Research and Development, 235 E 42nd St., New York, NY, 10017, USA

[2] Pfizer Global Research and Development, 10555 Science Center Dr, San Diego, CA 92121, USA

[3] Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK

[4] Pfizer Global Research and Development, 445 Eastern Point Road, Groton, CT 06340, USA

Corresponding author: Bharat Damle (Bharat.Damle@pfizer.com)

235 E 42nd St., New York, New York, 10017

Tel: (212) 733-4739

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ABSTRACT

Azithromycin (AZ) is a broad-spectrum macrolide antibiotic with a long half-life and a large volume of distribution. It is primarily used for the treatment of respiratory, enteric, and genitourinary bacterial infections. AZ is not approved for the treatment of viral infections, and there is no well-controlled, prospective, randomized clinical evidence to support AZ therapy in COVID-19 (Coronavirus Infectious Disease-2019). Nevertheless, there are anecdotal reports that some hospitals have begun to include AZ in combination with hydroxychloroquine (HCQ) or chloroquine (CQ) for treatment of COVID-19.

It is essential that the clinical pharmacology (CP) characteristics of AZ be considered in planning and conducting clinical trials of AZ alone or in combination with other agents, to ensure safe study conduct and to increase the probability of achieving definitive answers regarding efficacy of AZ in the treatment of COVID-19. The safety profile of AZ used as an antibacterial agent is well-established.(1) This work assesses published in vitro and clinical evidence for AZ as an agent with antiviral properties. It also provides basic CP information relevant for planning and initiating COVID-19 clinical studies with AZ, summarizes safety data from healthy volunteer studies, and safety and efficacy from Phase 2 and Phase 2/3 studies in patients with uncomplicated malaria, including a Phase 2/3 study in pediatric patients following administration of AZ and CQ in combination. This paper may also serve to facilitate the consideration and use of a priori-defined control groups for future research.

Pfizer clinical trials cited: A0661155 (NCT00367653); A0661157 (NCT00677833); A0661154 (NCT00282919); A0661134 (NCT00082576); A0661120 (NCT00074841); A0661158 (NCT01103063); A0661201 (NCT01103713); A0661126 (NCT00084227); A0661139; 066-191; 066-191B

INTRODUCTION

A single arm, non-randomized study in Marseilles, France suggested that HCQ alone or in combination with AZ reduced viral load in COVID-19 patients.(2) AZ was added to prevent bacterial super-infection in a subset of patients, while untreated patients from another center and those refusing treatment served as unmatched controls. At Day 6, 100% of patients (6/6) treated with HCQ and AZ had negative SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2) nasopharyngeal polymerase chain reaction (PCR) test, compared to 57.1% patients (8/14) treated with HCQ alone, and 12.5% controls (2/16) (p<0.001). The authors concluded in this study that HCQ was associated with viral load reduction and its effect was complemented by AZ. In a separate report (Preprint), subsequent single-arm study from the same center, 80 COVID-19 patients (including 6 patients from the prior study) received HCQ and AZ. A rapid fall in nasopharyngeal viral load tested by quantitative PCR (qPCR) was noted, with 83% negative at Day 7, and 93% at Day 8. Virus cultures from patient respiratory samples were negative in 97.5% patients at Day 5, which the authors noted was much earlier than untreated patients in prior cases.(3) The authors concluded that HCQ with AZ was potentially effective in reducing transmission and in the therapy of COVID-19.

To help determine the validity of these early clinical findings, it is important to understand if AZ demonstrates antiviral properties in vitro and in vivo, and the activity of AZ and HCQ in combination. AZ is a broad-spectrum macrolide antibiotic primarily used for the treatment of respiratory, enteric and genitourinary bacterial infections and has a well-established safety profile.(1) AZ is indicated for infections caused by susceptible bacterial pathogens in respiratory tract infections such as bronchitis and pneumonia. The minimum inhibitory concentrations (MIC_{90}) for AZ against most of these bacterial pathogens are ≤2.0 mg/L (2.67 µM).(1) The antibacterial mechanism of action of AZ is the binding to the 23S rRNA of the 50S ribosomal subunit of microorganisms, inhibiting bacterial protein synthesis and impeding the assembly of the 50S ribosomal subunit.(1) AZ is not approved for antiviral therapy but has been studied in vitro and in clinical trials for activity against several viruses. This review was undertaken to assess key AZ published data on in vitro antiviral activity and clinical studies across a variety of viral infections to support the design of future controlled studies.

Azithromycin Antiviral Properties In Vitro

Numerous investigations have reported in vitro antiviral activity of AZ against viral pathogens with 50% inhibitory concentrations ranging from approximately 1 µM to 6 µM, with the exception of H1N1 influenza (Table 1). The in vitro EC_{50} (50% effective concentration) for AZ against SARS-CoV-2, the virus responsible for COVID-19, was 2.12 µM (EC_{90}: 8.65 µM) following a 72-hour incubation period post-infection, with a ratio of infectious virions to cells in culture (multiplicity of infection; MOI) of 0.002.(4) In the same study, under the same experimental conditions, the in vitro EC_{50} for HCQ was 4.17 µM.

In other studies, the calculated in vitro EC_{50} for HCQ against SARS-CoV-2 ranged from 0.72 µM to 17.31 µM at a MOI from 0.01 to 0.8, measured at 48 hours post-infection.(5, 6) The selectivity index (SI) for HCQ is high, with a reported CC_{50} (50% cytotoxic concentration) of 250 µM.(6) In a pre-print study, following a 60-hour incubation period, a synergistic effect with the combination HCQ 2 µM + AZ 10 µM was observed in vitro on SARS-CoV-2 at concentrations expected in human lung, leading to total inhibition of viral replication.(7)

Caution should be exercised in comparing the EC_{50} values across these studies due to the differences in experimental conditions (eg, different cell lines, MOI, time of drug addition to culture, incubation times, and analytical methods).

Potential Mechanisms of Antiviral Activity

The precise mechanism is unknown; however, multiple mechanisms have been proposed for the putative antiviral properties observed with AZ. Endosome maturation and function require an acidic environment. AZ is a weak base and preferentially accumulates intracellularly in endosomal vesicles and lysosomes, which could increase pH levels, and potentially block endocytosis and/or viral genetic shedding from lysosomes thereby limiting viral replication.[15, 16] An acidic environment is also required for the uncoating of enveloped viruses such as influenza and human immunodeficiency virus (HIV) [17], and a similar mechanism is plausible for coronaviruses, also an enveloped virus. These mechanisms have also been proposed for the antiviral effect noted with HCQ and CQ [5, 6]; in fact, evidence suggests that AZ causes a more severe impairment of acidification than CQ.[15]

The putative antiviral effects of AZ may also be mediated by a global amplification of the host's interferon (IFN) pathway-mediated antiviral responses. Data suggest that AZ has the ability to induce pattern recognition receptors, IFNs, and IFN-stimulated genes) leading to a reduction of viral replication.[8, 14, 18] In addition, AZ directly acts on bronchial epithelial cells to maintain their function and reduce mucus secretion to facilitate lung function.[19]

Specific to SARS-CoV-2, recent quantum mechanical modeling suggests a potential role of AZ in interfering with viral entry via binding interaction between the SARS-CoV-2 spike protein and host receptor ACE2 (angiotensin converting enzyme-2) protein [20]; further experimental work on this is necessary to confirm the model.

Pharmacology

The pharmacokinetics of AZ are well understood. AZ is rapidly absorbed following oral administration, has a long serum half-life (68 hours)[1], and large volume of distribution (31 L/kg) [21]. AZ is taken up by leucocytes at concentrations that are about 300-fold higher than plasma.[22] In infected tissues, AZ concentrations are higher than in plasma, due to recruitment of leucocytes at the site of infection. Numerous studies have shown excellent penetration of AZ in a variety of infected tissues, and selected data pertinent to lung penetration are provided in Table 2.

Excellent tissue penetration in the lung allows for the treatment of respiratory infections for indicated bacterial pathogens for which the PK-PD target is linked to AUC/MIC. The PK-PD target(s) for the potential antiviral activity of AZ is unknown. Hence, for information purposes only, calculated ratios for C_{max} versus reported EC_{50} for SARS-CoV-2 are presented in Table 2.

As indicated (Table 2), lung tissue homogenates and alveolar macrophages have AZ concentrations well in excess of the EC_{50} for SAR-CoV-2, as well as for other respiratory viruses listed in Table 1, following approved doses of AZ. One limitation of these data is that concentrations in lung homogenates may not represent concentrations in infected cells.

Once in the lung, concentrations of AZ persist for several days after plasma concentrations become undetectable.(24, 26) The estimated terminal half-life in lung tissue and bronchial washings were 133 hours and 74 hours, respectively.(23) It is plausible that due to this unique pharmacokinetic property of AZ, coupled with target tissue concentrations in excess of in vitro EC_{50} against several viruses, AZ could play a potential therapeutic role in respiratory viral infections, including SARS-CoV-2.

Additional considerations for elderly patients may be applicable for COVID-19 infections. As per the product label, AZ exposures in geriatric patients were shown to be similar to those in young adults. In subjects with mild-to-moderate renal impairment, there was little increase in mean C_{max} (5.1%) and AUC_{0-120} (4.2%) following a single 1 g dose of AZ.(1) Dose adjustment is not considered to be required for geriatric patients with normal renal and hepatic function, however it should be noted that elderly patients may be more susceptible to the development of Torsades de Pointes.(1) In subjects with severe renal impairment, the mean AUC and C_{max} increased 35% and 61%, respectively, compared to subjects with normal renal function, thus caution should be exercised when dosing AZ in this population.(1)

Clinical Studies

Table 3 summarizes available clinical data on the efficacy of AZ alone, or in combination with other drugs, against various viral infections. With some exceptions, the studies in Table 2 have been observational, single-arm, non-randomized studies or retrospective evaluations. Many of these studies have reported clinical observations or conducted post-hoc analyses. Studies in COVID-19 patients

have mainly focused on viral load as an endpoint and detailed evaluation of clinical outcomes has not been reported. Notwithstanding the limitations of these studies, collectively they present preliminary evidence that inclusion of AZ in various treatment regimens can influence the course of viral infection and has the potential to influence clinical outcomes. Confirmatory evidence with randomized controlled trials is essential to understand the role of AZ in the treatment of COVID-19.

SAFETY

The safety profile of AZ used as an antibacterial agent is well-established and the risks associated with its use are minimized through provision of relevant information in product labelling (1) to support safe use of the product.

There have been numerous studies using dosing regimens of AZ and CQ either co-administered as separate tablets (AZ+CQ) or administered as fixed-dose combination tablets (AZCQ). These studies include three Phase 1 studies in healthy adult subjects; nine safety and efficacy Phase 2 or Phase 2/3 studies in adult patients with uncomplicated malaria; a single Phase 2/3 study in pediatric patients with uncomplicated *P. falciparum*; and two Phase 3 studies in asymptomatic pregnant women for intermittent preventative treatment of *P. falciparum* in pregnancy. Details of some of these studies are presented in Table 4.

From these studies, AZ+CQ at doses up to 2000 mg AZ and 600 mg CQ (base), administered for up to 3 days, was shown to be generally well-tolerated, safe in patients with uncomplicated malaria, and safe to be used in different age groups (age range from 18 to >75 years) including pediatric patients (age range from 6 months to 12 years) and pregnant women. However, at the higher doses (≥1500 mg) AZ was less well-tolerated due to AEs such as vomiting. In the studies in pregnant women, AZCQ combination therapy was less well-tolerated than sulfadoxine-pyrimethamine (SP); AEs such as vomiting, dizziness, headache, and asthenia were reported more frequently in the AZCQ treatment group than the SP group, and serious adverse events (SAEs) and discontinuations due to AEs were more frequent in the AZCQ treatment group. In general, the most frequently reported AEs associated with the treatment of AZCQ or AZ+CQ were generally gastrointestinal in nature and included

diarrhea, nausea, vomiting, and abdominal pain. Pruritus was also reported which was considered to be secondary to CQ. Prolonged cardiac repolarization and QT interval, which may impart a risk of Torsade de Pointes, has been seen in treatment with macrolides including AZ; CQ is also known to prolong the QT interval. In the studies presented in this document (Table 4), in a total of >2000 subjects exposed to 3-day regimens of AZ and CQ combinations, no relevant cardiovascular SAEs of concern were reported. Available data on the concomitant use of AZ and CQ in these studies indicated no increased risk of QT prolongation above that observed with CQ alone.

DISCUSSION

During drug development, it is essential to demonstrate robust in vitro evidence of activity prior to further study in humans. Subsequently, for a development candidate to have potential to elicit the desired effect over the necessary period of time in vivo, three fundamental 'pillars' need to be demonstrated (33):

1. Exposure at the target site of action over a desired period of time,

2. Binding to the pharmacological target as expected for its mechanism of action, and

3. Expression of pharmacological activity commensurate with the demonstrated target exposure and target binding.

The in vitro evidence presented here suggests that AZ has antiviral properties, including activity against SARS-CoV-2, at concentrations that are physiologically achievable with doses used to treat bacterial infections in the lung. One plausible mechanism for the antiviral properties is the intracellular sequestration of AZ resulting in an increase in endosomal and/or lysosomal pH. Lack of an optimal acidic environment in the intracellular milieu potentially attenuates viral replication. This mechanism is similar to that proposed for CQ and HCQ, and could explain how two drugs, both weak bases, can act in a complementary manner to inhibit viral replication. In a companion in vitro study by investigators in Marseilles, France, when AZ was dosed in combination with HCQ (2, 3), a synergistic effect was observed in vitro against SARS-CoV-2; however, no EC_{50} was determined.(7) The determination of in vitro EC_{50} for agents administered alone and in combination against SARS-

CoV-2 under similar experimental conditions is needed to further understand the putative antiviral effect of this combination. Other possible mechanisms including the amplification of the host's IFN pathway-mediated antiviral responses as well as AZ's potential to interfere with viral entry requires further experimental work.

Drugs known to interact with AZ, HCQ, or CQ are noted in their respective product labels.(1, 34, 35) In a study designed specifically to evaluate interaction between AZ and CQ, drug-drug interactions were not observed (36) and similar results would be expected with HCQ. CQ and HCQ are both substrates and potential inhibitors of P-glycoprotein (P-gp) (37-39); however, given that AZ is not a sensitive substrate of P-gp (40), potential inhibition of P-gp by HCQ would not be expected to significantly impact the systemic exposure of AZ as observed in the aforementioned study with CQ. Furthermore, CQ and HCQ are metabolized by multiple CYPs, including CYP3A, which AZ has not been shown to substantially modulate.(1, 41, 42) Although AZ has been shown to be an inhibitor of P-gp (43), AZ is unlikely to affect the lung penetration of HCQ, given that HCQ is highly permeable; thus P-gp efflux would not be expected to be rate-limiting. The lung penetration of HCQ in humans has not been reported; however, data in toxicology studies in albino rats, at human-equivalent plasma exposure, suggests HCQ distributes to the lung at concentrations of approximately 92 µM (44), which is far in excess of its EC_{50} values against SARS-CoV-2.(4)

A favorable clinical outcome is unlikely without clearance of the pathogen. However, translating the effect on viral (or bacterial) clearance into a clinical outcome in patients is confounded by the disease, variability in patients, design of the studies, and endpoints measured. This is apparent in the literature on clinical studies and observations with AZ in a variety of viral infections, which present a mixed picture of the utility of AZ dosed alone or with other drugs in the treatment of viral infection. Nonetheless, RNA-sequencing data from the MORDOR II (Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance) study on the reduction in both alpha- and beta-coronavirus burden and from the recent studies in COVID-19 patients (3) provides exploratory evidence on AZ, alone or in combination, against SARS-CoV-2, a novel beta-coronavirus.

AZ has been reported to exhibit anti-inflammatory activity.(45, 46) These effects are described as an acute phase inhibition of inflammation and a late phase of resolution of chronic inflammation. HCQ

also has anti-inflammatory properties and is approved for the treatment of lupus erythematosus and rheumatoid arthritis.(34) These effects, while unlikely to contribute to antiviral activity, could ameliorate the inflammatory processes caused by SARS-CoV-2 infection. Furthermore, as bacterial co-infection has been noted in COVID-19 patients, AZ may have a role in treatment of indicated pathogens.

Although not an approved indication, the combination of AZ and CQ was well-tolerated in healthy subjects and patients infected with malaria. Available data on the concomitant use of AZ and CQ in these studies indicated no increased risk of QT prolongation above that of CQ alone. In a recent preprint (47), it was reported that in COVID-19 patients (N=84), 11% of patients treated with an unspecified dose regimen of HCQ and AZ had recorded QT intervals >500 msec and 12% of patients had a change from Baseline of >60 msec; there were no events of Torsade de Pointes recorded.

In conclusion, the literature presented here provides a foundation for the study of AZ combined with HCQ in prospective randomized clinical trials or other control methods defined a priori for the treatment of COVID-19 that evaluate clinical outcomes, in addition to reductions in viral burden. As of 8 April 2020, there are 19 studies listed on clinicaltrials.gov using the search terms 'azithromycin' and 'COVID-19' that will further examine the use of AZ.

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Table 1.   In Vitro Antiviral Activity of Azithromycin

Targeted Virus	Antiviral Activity Screening System	Time of Drug Addition to Infected Cell Culture	Incubation Period	MOI	IC_{50} OR EC_{50} (μM)	CC_{50} (μM)	SI^a	Reference
SARS-CoV-2	Vero cells	15 min pre-treatment	72 h	0.002	2.12 EC_{90}: 8.65	>40	>19	(4)
Zika	Vero cells	12 h pre-treatment	48 h	0.1	6.59	810	123	(8)
	Huh7 cells				1.23-4.97	1360	>273	
	A549 cells				4.44	-		
	Hela cells				-	3560		
	U87 cells	>1 h pre-treatment	48 h	0.01	2.1	53	25	(9)
				0.1	2.9		18	
				3.0	5.1		10	
	Astrocytes			1.0	15	44	2.9	
Ebola	Ebola VLP entry assay (Hela cells)	1 h pre-treatment	2 h	N/A	2.79 IC_{90}: 15.8	>500	>179	(10)
	Ebola pseudovirion entry assay (Hela cells)	8 h pre-treatment	72 h	N/A	0.69 IC_{90}: 4.16	-	-	(11)
	Pseudotype Ebola entry assay (Hela cells)	1 h pre-treatment	19 h	N/A	1.3			(12)

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	Ebola replication assay (Vero 76 cells)		48 h	0.2	5.1	>130	>25	
Influenza (H1N1)	A549 cells	Simultaneous	48 h	1.0	68	>600	>8.8	(13)
Dengue (Serotype 2)	Vero cells	12 h pre-treatment	48 h	0.01	3.71	810	218	(8)
Rhinovirus	Human bronchial epithelial cells	24 h pre-treatment	48 h	1.0	IC_{50} not calculated; RV replication was inhibited at 10 μM and 50 μM (p<0.01)	-	-	(14)

a. reported or calculated

CC_{50}=50% cytotoxic concentration; EC_{50}=50% effective concentration; EC_{90}=90% effective concentration; h=hour; IC_{50}=50% inhibitory concentration; IC_{90}= 90% inhibitory concentration; MOI=multiplicity of infection; N/A=not applicable; RV=rhinovirus; SI=selectivity index (CC_{50}/IC_{50}); VLP=virus-like particle

Table 2.   Pharmacokinetics of Azithromycin in Plasma, Serum, and Lung

AZ dose	Matrix	AUC (mg.h/L)	C_{max} (mg/L)	Ratio[a] C_{max}/EC_{50}	Reference
500 mg daily x 3 days	Plasma	20.48	0.26	0.16	(23)
	Bronchial washings	60.6	0.72	0.45	
	Lung tissue homogenate	1318	9.13	5.75	
1000 mg daily x 3 days	Plasma	25.6	0.32	0.20	(23)
	Bronchial washings	135.1	1.41	0.89	
	Lung tissue homogenate	2502	17.85	11.24	
500 mg daily x 3 days	Plasma	11.62	0.18	0.11	(24)
	Bronchial washings	70.29	0.83	0.52	
	Lung tissue homogenate	1245.4	8.93	5.62	
1000 mg daily x 3 days	Plasma	19.83	0.32	0.20	(24)
	Bronchial washings	139.9	1.49	0.94	
	Lung tissue homogenate	2514.2	18.6	11.71	
500 mg single dose	Serum	3.1	0.39	0.25	(25)
	Epithelial lining fluid	18.8	1.2	0.76	
	Lung tissue homogenate	432	8.3	5.23	
	Alveolar macrophages	5804	194	122.18	

a. Ratio calculated using molecular weight of AZ of 749 and in vitro EC_{50} against SARS CoV-2 of 2.12 µM (4):

 (X mg/L × (1 mol/749.0 g) × 1000) / 2.12 mg/L.

AUC=area under the curve; C_{max}=maximum concentration; EC_{50}=50% effective concentration.

Table 3.   Selected Clinical Studies in Respiratory Viral Infections

Study Population	Study design	Treatments	Key Results	Conclusion	Reference
COVID-19, >12 yrs (N=36)	Observational, non-randomized, external control, open-label	• Non-randomized Control • HCQ (200 mg q8h x 10 days) • HCQ + AZ (500 mg D1 and 250 mg D2-5)	At D6 post-inclusion, negative nasopharyngeal PCR in: 100% (6/6) pts. HCQ + AZ 57.1% (8/14) HCQ 12.5% controls (p<0.001).	The authors concluded that HCQ is significantly associated with viral load reduction and its effect is reinforced by azithromycin. Additional studies are needed in more severe patient population (NEWS score) with a robust control group.	(2)
COVID-19, >18 yrs (N=80)	Observational, single arm	• HCQ (200 mg q8h x 10 days) + AZ (500 mg D1 and 250 mg D2-5)	Decrease in nasopharyngeal viral load (qPCR): 83% negative at D7, and 93% at D8. Patients presumably contagious (PCR Ct <34) decreased and reached zero on D12.	The authors concluded that these results corroborated the efficacy of HCQ with AZ and its potential effectiveness in the early impairment of contagiousness. This finding provides further evidence in uncontrolled case series, deserving replication.	(3)
COVID-19, 20-77 yrs, (N=11)	Observational, single arm	• HCQ + AZ (unspecified doses)	Within 5 days, one patient died, two were transferred to the ICU. One patient discontinued after 4 days due to QT interval of 460 msec to 470	No evidence of strong antiviral activity with the combination of HCQ and AZ.	(27)

Table 3.   Selected Clinical Studies in Respiratory Viral Infections

Study Population	Study design	Treatments	Key Results	Conclusion	Reference
			msec (baseline 405 msec). At D6, 8/10 patients were positive for SARS-CoV-2 RNA in nasopharyngeal swabs.		
Healthy children <5 yrs (N not specified)	Ad hoc analysis of an interventional, randomized, cluster-controlled, blinded study.	• Placebo • AZ suspension every 6 months for 2 years	At 24 months, an 8x reduction (via RNA-seq) in alpha-coronavirus and a 14x reduction in beta-coronavirus in AZ group vs placebo. At 36 months, number of children with coronavirus was not different between groups.	AZ may decrease viral load but not prevalence of colonization.	MORDOR II Study[b]
MERS (N=349)	Retrospective, multicenter cohort database	• Macrolide, n=136 (39%), [71.3% with AZ] • No macrolide	90-day mortality (adjusted OR: 0.84; 95% CI 0.47–1.51) or MERS-CoV RNA clearance (adjusted HR: 0.88; 95% CI: 0.47–1.64).	Macrolide therapy was not associated with a reduction in 90-day mortality or improvement in MERS-CoV RNA clearance.	(28)
Confirmed SARS (2003) 16-84 yrs	Retrospective review	• Ribavirin+C/S (N=40) • FQ+AZ+IFN-α	Early use of high-dose steroids with a quinolone plus azithromycin showed improvement of clinical symptoms	The early use of high-dose steroids with a quinolone plus azithromycin gave the best	(29)

Table 3.   Selected Clinical Studies in Respiratory Viral Infections

Study Population	Study design	Treatments	Key Results	Conclusion	Reference
(N=190)		[+steroid] (n=30) • Q+AZ [+IFN-α + steroid] (n=60) • Levo+AZ [+IFN-α + steroid] (n=60)	and signs and a decreased incidence of ARDS, mechanical ventilation, and mortality Respiratory improvement and mean time to discharge was shorter in Q + AZ and Levo + AZ groups.	clinical outcome.	

Table 3.   Selected Clinical Studies in Respiratory Viral Infections

Study Population	Study design	Treatments	Key Results	Conclusion	Reference
Influenza A infection, >20 yrs (N=107)	Prospective, randomized, controlled, open-label, multicenter	• Oseltamivir (75 mg q12h x 5 days) (n=56) • Oseltamivir (75 mg q12h x 5 days) + AZ (2000 mg single dose extended release) (n=51)	No significant treatment differences in inflammatory markers. Trends in favor of combination therapy for reduction in max temp on D3-5 (p=0.048); improvement in sore throat on D2.	Combination therapy showed an early resolution of some symptoms.	(30)
Diagnosed for Influenza-A (H1N1) pdm09 strain (N=329)	Retrospective chart review	• Oseltamivir • Oseltamivir + AZ (500 QD)	Monotherapy vs combination: secondary bacterial infections (23.4% vs 10.4%), length of hospitalization (6.58 vs 5.09 days), incidences of respiratory support (38.3% vs 17.6%), influenza symptom severity score D5 (12.7 vs 10.7)	Combination therapy was more efficacious compared to oseltamivir alone in rapid recovery of influenza-associated complications in high-risk patients.	(31)
RSV Otherwise healthy infants (N=40)	Randomized, double-masked, placebo-controlled, proof-of-concept	• AZ • Placebo (14 days)	Azithromycin did not reduce serum IL-8 levels at D8 (p=0.6) but reduced nasal lavage IL-8 by D15 (p=0.03). $\geq$3 wheezing episodes (22% in AZ vs 50% in placebo) (p=0.07).	Azithromycin treatment during RSV bronchiolitis reduced upper airway IL-8 levels, prolonged the time to the third wheezing episode and reduced overall respiratory morbidity.	(32)

Table 3.   Selected Clinical Studies in Respiratory Viral Infections

Study Population	Study design	Treatments	Key Results	Conclusion	Reference
a. In press: Doan T, Hinterworth A, Arzika A, et al. Reduction of coronavirus burden with mass azithromycin distribution.					
ARDS=Acute Respiratory Distress Syndrome; AZ=azithromycin; CI=confidence interval; CoV=coronavirus; COVID-19=Coronavirus Infectious Disease-2019; C/S=cefoperazone/sulbactam; D=Day; FQ=fluoroquinolone; HCQ= hydroxychloroquine; IFN=interferon; IL=interleukin; Levo=levofloxacin; MERS=Middle East Respiratory Syndrome; N=number of patients; n=subgroup or subpopulation; NEWS=National Early Warning Score; OR=odds ratio; PCR=polymerase chain reaction; Q=quinolone; QD=once daily; qPCR=quantitative PCR; RSV=respiratory syncytial virus; SARS=Severe Acute Respiratory Syndrome; vs=versus; yrs=years old.					

Table 4.   Summary of Azithromycin and Chloroquine Combination Studies

Study Code and Study Title	Age Range of Treated Subjects	Dose Regimen (Number Tested)	Safety Summary
A0661139: A Multiple-Dose Study to Assess the Effects of Azithromycin plus Chloroquine on Electrocardiograms in Healthy Subjects	Adults, age 18 to 55 years	5 treatment groups; each treatment administered for 3 days: (1) 600 mg CQ (N = 24) (2) 600 mg CQ + 500 mg AZ (N = 24) (3) 600 mg CQ + 1000 mg AZ (N = 24) (4) 600 mg CQ + 1500 mg AZ (N = 23) (5) placebo (N = 24)	Most AEs were mild or moderate; no SAEs were reported which were considered related to study drug. Three subjects in the 1500 mg AZ+CQ group discontinued due to AEs (diarrhea; loss of appetite; nausea, diarrhea and vomiting). AE rates were similar across the combination treatment groups. although events of diarrhea, nausea and vomiting were greater in the higher dose groups. The primary endpoint was change from Baseline in triplicate ECG measurements at each of 10 time points post-dose on Day 3 vs time-matched triplicate ECGs on study Day -1 (Baseline). Maximum mean increases in QTcF versus placebo of approximately 35 to 37 msec were similar among all AZ+CQ and CQ alone treatments. In comparison to CQ alone, the maximum mean (90% CI) increases in QTcF were approximately 5.3 (0.2, 10.4) msec, 6.5 (1.4, 11.6) msec and 8.9 (3.6 , 14.2) msec for the 500 mg, 1000 mg and 1500 mg AZ+CQ groups, respectively. Mean changes from time-matched baseline QTcF (compared to placebo alone) ranged from 18.4 msec to 35.0 msec in the CQ alone group; 21.5 msec to 36.2 msec in the 500 mg AZ+CQ group; 19.9 msec to 36.9 msec in the 1000 mg AZ+CQ group; and from 20.2 msec to 35.3 msec in the 1500 mg AZ+CQ treatment group.

a

066-191: A Randomized, Double Blind, Comparative Study of Azithromycin vs Chloroquine as Treatment of Plasmodium falciparum and Plasmodium vivax Malaria	Adults, age 18 to 60 years (AZ) and 18 to 45 years (CQ)	2 treatment groups: (1) 1000 mg AZ; once daily for 3 days (N = 16) (2) 600 mg CQ once daily on Days 1 and 2, then 300 mg CQ on Day 3 (N = 16) (due to poor activity of either agent alone against *P. falciparum*, study was modified to 066-191B)	Two subjects treated for *P. vivax* were discontinued from the study due to AEs related to CQ (maculopapular rash [moderate], pruritus [severe]) There was 1 treatment-related SAE of urticaria in the AZ treatment group.
066-191B: A Randomized, Double Blind, Comparative Study of Azithromycin vs Chloroquine as Treatment of Plasmodium Falciparum and Plasmodium vivax Malaria	Adults, age 18 to 55 years	1000 mg AZ + CQ (600 mg days 1 and 2, and 300 mg on day 3), for 3 days (N = 64)	There were no SAEs following treatment with AZ+CQ, and no discontinuations due to AEs. Treatment with AZ+CQ was better tolerated than monotherapy with AZ or CQ alone in subjects with *P. falciparum* malaria.

A0661120: A Phase 2/3, Randomized, Comparative Trial of Azithromycin Plus Chloroquine Versus Sulfadoxine-Pyrimethamine Plus Chloroquine for the Treatment of Uncomplicated Plasmodium falciparum Malaria in India	Adults, age 18 to 75 years (AZ+CQ) and 18 to 60 years (SP+CQ)	3 treatment groups: (1) 1000 mg AZ + 600 mg CQ; once daily, for 3 days (N = 83) (2) 500 mg AZ + 600 mg CQ; once daily, for 3 days (N = 67) (3) 1500 mg/75 mg sulfadoxine-pyrimethamine (SP) on Day 0, 600 mg CQ on Days 0 and 1, and 300 mg on Day 2 (N = 80)	Fewer than 10% subjects in all 3 groups reported treatment-related AEs, and no subjects discontinued the study due to AEs related to study drug. One subject reported a treatment-related SAE ("abnormal behaviour") in the SP+CQ group which was attributed to CQ. All treatment-related AEs occurred at an incidence of <5% (≤4) subjects (vomiting, diarrhea, abdominal pain, pruritis, gastritis) and all were mild or moderate. In the 500 mg AZ+CQ group, 1 (1.5%) subject reported vomiting and 1 (1.5%) subject reported pruritus. In the 1000 mg AZ+CQ group, vomiting was reported by 4 (4.8%) subjects and pruritus was reported by 2 (2.4%) subjects. In addition, 2 (2.4%) subjects reported abdominal pain, and diarrhea and gastritis were reported by 1 (1.2%) subject each.
A0661126: A Phase 2/3, Randomized, Double Blind, Comparative Trial of Azithromycin Plus Chloroquine Versus Atovaquone-Proguanil for The Treatment of Uncomplicated Plasmodium falciparum Malaria In South America	Adults, aged 18 to 86 years (AZ+CQ) and 18 to 74 years (A-P)	3 treatment groups; each treatment administered for 3 days: (1) 1000 mg AZ + 600 mg CQ (N = 114) (2)[b] 500 mg AZ + 600 mg CQ (N = 14) (3) 1000 mg atovaquone + 400 mg proguanil [A-P] (N = 116)	One subject in the 1000 mg AZ+CQ treatment group discontinued due to a treatment-related AE of vomiting. The treatment-related AEs most frequently reported by subjects treated with 500 mg AZ+CQ were pruritus (4 subjects; 28.6%), gastritis (1 subject [7.1%]) and mouth ulceration (1 subject [7.1%]); and with 1000 mg AZ+CQ were pruritus (28 subjects; 24.6%), diarrhea/loose stools (8 subjects [7.1%]), and paresthesia (6 subjects [5.3%]). Most events were mild to moderate; 3 treatment-related AEs were assessed as severe: pruritus (1000 mg AZ+CQ), gastritis (500 mg AZ+CQ) and abdominal pain (A-P). There were no treatment-related SAEs. The incidence of AEs was higher in the AZ combination treatment groups than in the A-P group and was attributed primarily to the incidence of pruritus which is secondary to CQ treatment.

A0661134: A Phase 2/3, Randomized, Double-Blind, Comparative Trial of Azithromycin Plus Chloroquine Versus Mefloquine for the Treatment of Uncomplicated Plasmodium falciparum Malaria in Africa	Adults, aged 18 to 63 years (AZ+CQ) and 18 to 68 years (mefloquine)	3 treatment groups: (1) 1000 mg AZ + 600 mg CQ, once daily for 3 days (N = 114) (2)[b] 500 mg AZ + 600 mg CQ, once daily for 3 days (N = 9) (3) 750+500 mg mefloquine on Day 0 (N = 115)	Most frequently reported treatment-related AEs with 500 mg AZ+ CQ were pruritus (2 subjects [22.2%]), abdominal pain (1 subject [11.1%]), dyspepsia (1 subject [11.1%]), loose stools (1 subject [11.1%]), and vomiting (1 subject [11.1%]); and with 1000 mg AZ+CQ were pruritus (58 subjects [50.9%]), vomiting (18 subjects [15.8%]), and headache (15 subjects [13.2%]); the majority of AEs were mild. There was 1 severe treatment-related AE of vomiting in the 1000 mg AZ+CQ treatment group and 2 subjects from this treatment group discontinued the study due to vomiting and vomiting/ dizziness/tinnitus. There were no SAEs which were considered related to AZ+CQ.
A0661154: A Phase 2, Open Label, Non-Comparative Trial of Azithromycin 2000 mg Plus Chloroquine 600 mg base Daily for Three Days for the Treatment of Uncomplicated Plasmodium falciparum Malaria	Adults, aged 18 to 77 years	2000 mg AZ + 600 mg CQ (N = 110), each administered for 3 days	Most frequently reported treatment-related AEs were nausea (30.0%), vomiting (18.2%), and diarrhea (11.8%) which were all mild or moderate with the exception of 1 severe event of vomiting. There were no SAEs or discontinuations due to AEs. Triplicate ECGs were measured on Days 0 (pre-dose), Days 1 and 2 (pre- and post-dose) and on Days 3 and 7. Mean increases in QTcF from baseline ranged from 12 msec to 49.9 msec and overall, 30 (29%), 6 (6%), and 2 (2%) subjects met the criteria of absolute QTcF values of 450 to <480 msec, 480 to <500 msec, and ≥500 msec, respectively. The QTcF prolongation observed was consistent with that reported for CQ alone and for AZ+CQ in previous studies. Co-administration of AZ did not worsen the QT prolongation associated with CQ

A0661155: A Phase 3, Randomized, Open-Label, Comparative Trial of Azithromycin Plus Chloroquine Versus Mefloquine for the Treatment of Uncomplicated Plasmodium Falciparum Malaria in Africa	Adults, aged 17 to 58 years (AZ+CQ) and 18 to 71 years (mefloquine)	2 treatment groups: (1) 1000 mg AZ + 600 mg CQ (N = 113), once daily for 3 days (2) 750+500 mg mefloquine (N = 116)	There were no SAEs in the AZ+CQ treatment group and all AEs in the AZ+CQ group were mild or moderate. One subject in this group discontinued due to an AE of pruritus. The most frequently reported treatment-related AEs in the AZ+CQ group were pruritus (28.3%), headache (17.7%), dizziness (15.9%), abdominal pain (11.5%), nausea (8.8%), and vomiting (3.5%).
A0661157: Phase 2/3, Open-Label, Comparative Trial of Azithromycin Plus Chloroquine versus Artemether-Lumefantrine for the Treatment of Uncomplicated Plasmodium Falciparum Malaria in Children in Africa	Children, aged 6 months to 12 years (both treatment groups)	2 treatment groups, each treatment administered for 3 days: (1) AZCQ fixed-dose combination tablet[c] (N = 179) (2) artemether-lumefantrine (AL) 20 mg/120 mg (N = 182)	There were no SAEs considered to be related to study treatment and no permanent discontinuations from the study due to AEs; subjects discontinued from dosing more frequently in the AZCQ group, mostly due to vomiting. Most AEs were mild or moderate. Vomiting and pruritus were more frequently reported in the AZCQ cohorts than the AL cohorts. The most frequently reported treatment-related AEs (≥5%) in the AZCQ cohorts were vomiting, abdominal pain, parasitemia, malaria, pyrexia and pruritus. The QTc changes observed in this study were similar to those reported in African children with uncomplicated malaria treated with AL, SP, or CQ. The only AE reported was one of mild QT prolongation in a subject treated with AL, who had concurrent pyrexia.

A0661158: Phase 3, Open-Label, Randomized, Comparative Study to Evaluate Azithromycin plus Chloroquine and Sulfadoxine plus Pyrimethamine Combinations for Intermittent Preventive Treatment of Falciparum Malaria Infection in Pregnant Women in Africa	Pregnant subjects, aged 16 to 35 years (both treatment groups)	2 treatment groups: (1) 1000 mg/620 mg AZCQ (4x fixed-dose combination tablet[d]), for 3 treatment days (N = 1446) (2) 1500 mg/75 mg SP (3x 500 mg/25 mg tablets on Day 0) (N = 1445)	Maternal group There were 3 (0.2%) deaths in the AZCQ group and 1 (0.1%) in the SP group, but none were considered related to study drug. Most treatment-related AEs were mild or moderate; 0.9% in the AZCQ group were considered severe. Five (0.3%) subjects had SAEs which were considered related to AZCQ (vomiting [3], dizziness [2], diarrhea and asthenia [1 each]). The most common treatment-related AEs in the AZCQ group were vomiting (44.6%), dizziness (31.4%), headache (15.3%) and asthenia (15.2%), diarrhea (14.2%), nausea (14.2%), and blurred vision (10.0%). Neonatal group There were 25 (2.2%) neonatal deaths in the AZCQ group and 22 (1.8%) in the SP group but no deaths were considered related to study drug. There were no SAEs considered related to study drug. Treatment-related AEs in neonates exposed in utero to AZCQ were low birth weight baby (0.2%), anemia (0.1%), and jaundice neonatal (0.1%).

A0661201: An Open Label, Non-Comparative Study To Evaluate Parasitological Clearance Rates And Pharmacokinetics Of Azithromycin And Chloroquine Following Administration Of A Fixed Dose Combination Of Azithromycin And Chloroquine (AZCQ) In Asymptomatic Pregnant Women With Plasmodium Falciparum Parasitemia In Sub-Saharan Africa	Pregnant subjects, aged 16 to 34 years	1000 mg/620 mg AZCQ fixed-dose combination tablet[d], for 3 treatment days (N = 168)	Maternal group No deaths occurred in the maternal group. The most common treatment-related AEs occurring in ≥5 subjects were vomiting (20.2% subjects), dizziness (19.6% subjects), pruritus (7.1% subjects), headache and generalized pruritus (5.4% subjects each), fatigue (4.2% subjects), and nausea (3.6% subjects). All maternal TEAEs were mild or moderate. No SAEs were reported which were related to study drug and no AEs leading to discontinuations from the study Neonatal group No treatment-related AEs were reported for the neonatal group. There were 4 deaths, none of which were considered related to study drug. No SAEs were reported which were related to study drug

a. For all CQ treatment administered in the studies in this table, CQ is noted as base amounts; eg, 600 mg CQ base derived is from 1000 mg CQ

b. Treatment arm discontinued due to high failure rate of that arm

c. AZCQ fixed dose combination: 300 mg AZ and 100 mg CQ or 150 mg AZ and 50 mg CQ; tablets scored to allow for dosing by body weight

d. AZCQ fixed dose combination tablet: 250 mg AZ and 155 mg CQ

Abbreviations: AE=adverse event; AL=artemether-lumefantrine; A-P=atovaquone + proguanil; AZ=azithromycin; AZCQ=fixed-dose combination of azithromycin and chloroquine; CQ=chloroquine; ECG = electrocardiogram; SP=sulfadoxine-pyrimethamine; SAE=serious adverse event; TEAE=treatment-emergent adverse event