FDA Introductory Comments

NDA 210795: Tafenoquine for the radical cure of *Plasmodium vivax* malaria

Antimicrobial Drugs Advisory Committee Meeting
July 12, 2018

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FDA

Introduction

- NDA 210795: Tafenoquine tablet
- Applicant: GlaxoSmithKline
- Orphan Drug and Breakthrough Therapy designations for the radical cure of *P. vivax* malaria
- NDA granted priority review
- Primaquine (PQ) 15 mg daily x14 days is the only approved drug for the radical cure of *P. vivax* malaria

Proposed Dosing

A single 300 mg dose (two 150 mg tablets) on the first or second day of an appropriate therapy for the acute *P. vivax* malaria infection, e.g. chloroquine (CQ)

Development Program

- Three randomized, double-blind efficacy/safety trials:
  - Two trials compared tafenoquine (TQ) 300 mg single dose in combination with CQ to CQ alone
    - 582 Part 1 (Phase 2b)
    - 582 Part 2 (Phase 3)
  - A safety trial 564 comparing TQ 300 mg single dose + CQ to PQ (14 days) + CQ provided supportive efficacy information
- Three safety studies in healthy volunteers
  - Ophthalmic safety study
  - Cardiac safety study
  - Safety study in G6PD normal and deficient individuals

Efficacy

- In two trials 582 part 1 and part 2, TQ 300 mg single dose in combination with CQ was superior to CQ alone for the relapse-free efficacy endpoint at 6 months
  - Part 1: CQ+TQ 89% vs CQ 37%, difference 52%, 95%CI (35%, 69%), p <0.001
  - Part 2: CQ+TQ 60% vs CQ 26%, difference 33%, 95%CI (23%, 43%), p <0.001

- In the supportive trial 564, TQ 300 mg single dose in combination with CQ was compared to PQ + CQ combination for the relapse-free efficacy at 6 months
  - CQ+TQ 67% vs CQ+PQ 71%, difference -3.4%, 95%CI (-16.0,9.8)

Safety

- In three Phase 2/3 trials, 483 *P. vivax* malaria patients were exposed to TQ 300 mg single dose in combination with CQ
  - Hemolysis/decrease in hemoglobin/methemoglobinemia
- In healthy volunteer studies, 401 subjects were exposed to TQ at 300 mg single dose
  - Hemolysis/decrease in hemoglobin/methemoglobinemia
    - Dose dependent
    - G6PD level dependent
  - Hypersensitivity
  - Psychiatric adverse reactions
  - No ocular safety risk
  - No QT prolongation potential

Outline for the Day

- Presentations by the Applicant
- Presentations by the FDA
  - **Efficacy** by Xianbin Li, Ph.D.
  - **Safety** by Elizabeth O'Shaughnessy, M.D.
- Clarifying Questions
- Lunch
- Open Public Hearing
- Questions to the committee

Question 1

- Has the applicant provided substantial evidence of the effectiveness of tafenoquine for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients 16 years of age and older?
  - If yes, please provide any recommendations concerning labeling.
  - If no, what additional studies/analyses are needed?

Question 2

- Has the applicant provided adequate evidence of the safety of tafenoquine for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients 16 years of age and older?
  - If yes, please provide any recommendations concerning labeling.
  - If no, what additional studies/analyses are needed?

U.S. FOOD & DRUG ADMINISTRATION

NDA 210795 Tafenoquine Efficacy Review

Xianbin Li, Ph.D.
Statistical Reviewer
Division of Biometrics IV

Efficacy Studies Reviewed

- Indication: the radical cure (eradication of the hypnozoite stage) of *Plasmodium (P) vivax*
- Dose: Tafenoquine (TQ) 300 mg, single-dose given with Chloroquine (CQ) therapy
- 3 multi-center, double-blind, double-dummy, randomized studies
  - Study 582 Part 1: dose ranging, placebo and active-controlled
  - Study 582 Part 2: placebo- and active-controlled study
  - Study 564: Active-controlled study
- All 3 studies supported efficacy of TQ

Study 582 Part 1: Design

- Conducted in Brazil, India, Peru, and Thailand.
- Randomized equally to 6 groups:
  - Four CQ+TQ groups (50, 100, 300, and 600 mg), single dose on Day 1 or 2
  - CQ+PQ (primaquine) once daily for 14 days (Days 2 to 15) (active control)
  - CQ alone (placebo)
- All subjects received CQ (Day 1 to 3) for blood-stage infection.

Study 582 Part 1: Design

- Inclusion Criteria
  - Positive Giemsa smear for *P. vivax*
  - Parasite density >100 and <100,000/µL
  - Age ≥16 years
- Exclusion Criteria
  - Mixed malaria infections
  - Severe *P. vivax* malaria as defined by World Health Organization (WHO) criteria
  - Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency

Study 582 Part 1: Efficacy Endpoint

- Relapse-free efficacy at 6 months: initial clearance of parasitemia, defined as 2 smear slides 6-12 hours apart, with no presence of *P. vivax* asexual stage parasites within 6 months

Study 582 Part 1: Analysis Methods

- Intent-to-Treat (ITT): all randomized subjects.
- Kaplan-Meier estimate and log-rank test: primary analysis for time to relapse
- Multiple comparisons: a closed testing approach was used (i.e. hypotheses were tested in order from highest to lowest dose)

Study 582 Part 1: Baseline

	CQ	CQ+TQ				CQ+PQ
		50 mg	100 mg	300 mg	600 mg	
Randomized (ITT)	54	55	57	57	56	50
Males, n(%)	39 (72)	37 (67)	44 (77)	43 (75)	45 (80)	35 (70)
Mean age (yrs)	33.6	36.3	34.6	36.2	35.7	36.0
P. vivax - asexual parasite count, n(%)						
≤7500/µL	37 (69)	38 (69)	41 (72)	37 (65)	35 (63)	36 (72)
>7500/µL	17 (31)	17 (31)	16 (28)	20 (35)	21 (38)	14 (28)

Study 582 Part 1: 6-month Results

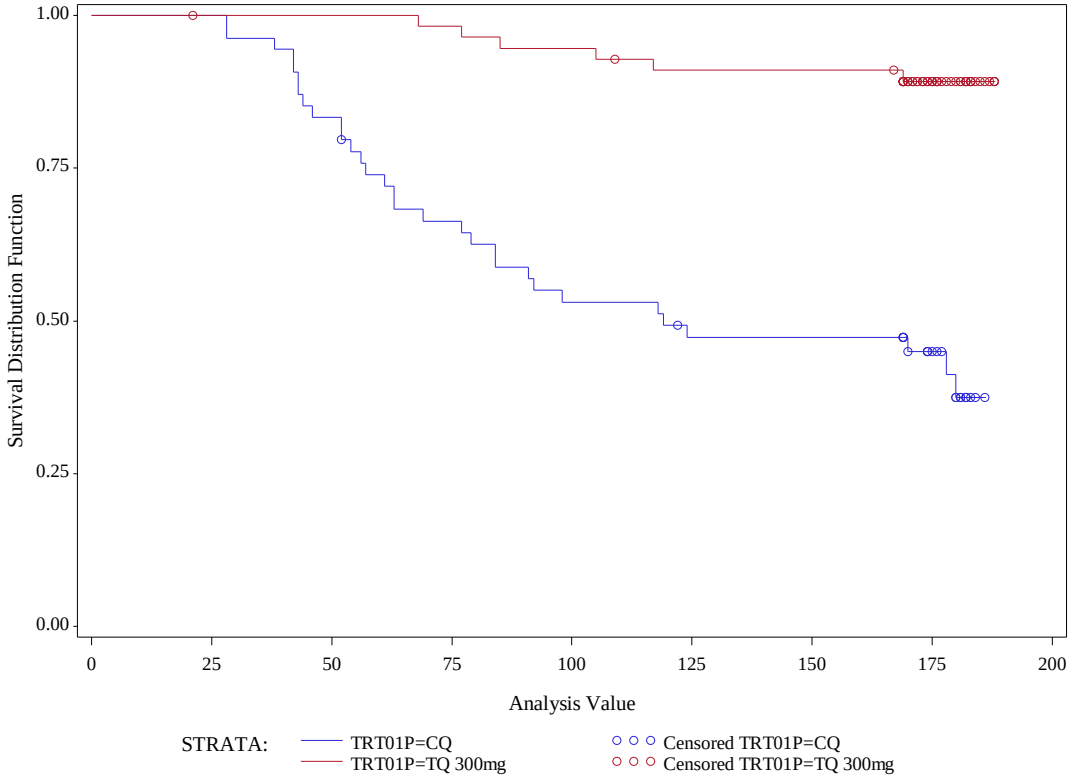
	CQ	CQ+TQ				CQ+PQ
		50 mg	100 mg	300 mg	600 mg	
Relapse-free efficacy at 6 months, n(%)	21 (39)	29 (53)	29 (51)	48 (84)	43 (77)	34 (68)
Relapse, n(%)	31 (57)	22 (40)	25 (44)	6 (11)	4 (7)	12 (24)
Censored[a], n(%)	2 (4)	4 (7)	3 (5)	3 (5)	9 (16)	4 (8)

a. Subjects were censored if they did not have *P. vivax* at baseline, took an anti-malarial drug or did not have a 6-month assessment

Study 582 Part 1: 6-month KM Results

Relapse-free efficacy at 6 months from Kaplan-Meier Method	CQ	CQ + TQ 300 mg
Estimate (%)	38	89
95% CI (%)	23, 52	77, 95
Difference in proportions (95% CI)		52 (35, 69)
P-value from Log-rank test		<0.0001

Study 582 Part 1: 6-month KM Curves



Study 582 Part 1: Additional Analyses

- Subgroup analyses showed consistent treatment effects across age, sex, race, weight, country, and baseline parasite count.
- Analysis of relapse-free efficacy at 4 months produced similar results as at 6 months.

Study 582 Part 1: Conclusion

- The selected 300-mg TQ + CQ group demonstrated statistically significantly improved efficacy compared with the CQ alone control group.

Study 582 Part 2: Design

- Conducted in Brazil, Ethiopia, Cambodia, Peru, Philippines and Thailand
- Subjects were randomized 1:2:1 to
  - CQ alone (placebo)
  - CQ + TQ (Days 1 or 2) 300 mg
  - CQ + PQ (once daily for 14 days)

  All subjects received CQ on Days 1 to 3.
- Inclusion and exclusion criteria very similar to Part 1

Study 582 Part 2: Efficacy Endpoint

- Recurrence-free at 6 months: initial clearance of *P. vivax* parasitemia, defined as 2 negative asexual *P. vivax* parasite counts, with at least 6 hours between counts, no positive counts in the interval, and up to Day 201.

Study 582 Part 2: Analysis Methods

- Microbiologic ITT (micro-ITT): all randomized subjects who received at least 1 dose of study medication and had a positive parasite smear of *P. vivax* at baseline
- Kaplan-Meier analysis and Cox proportional hazards model (with region and treatment as covariates)

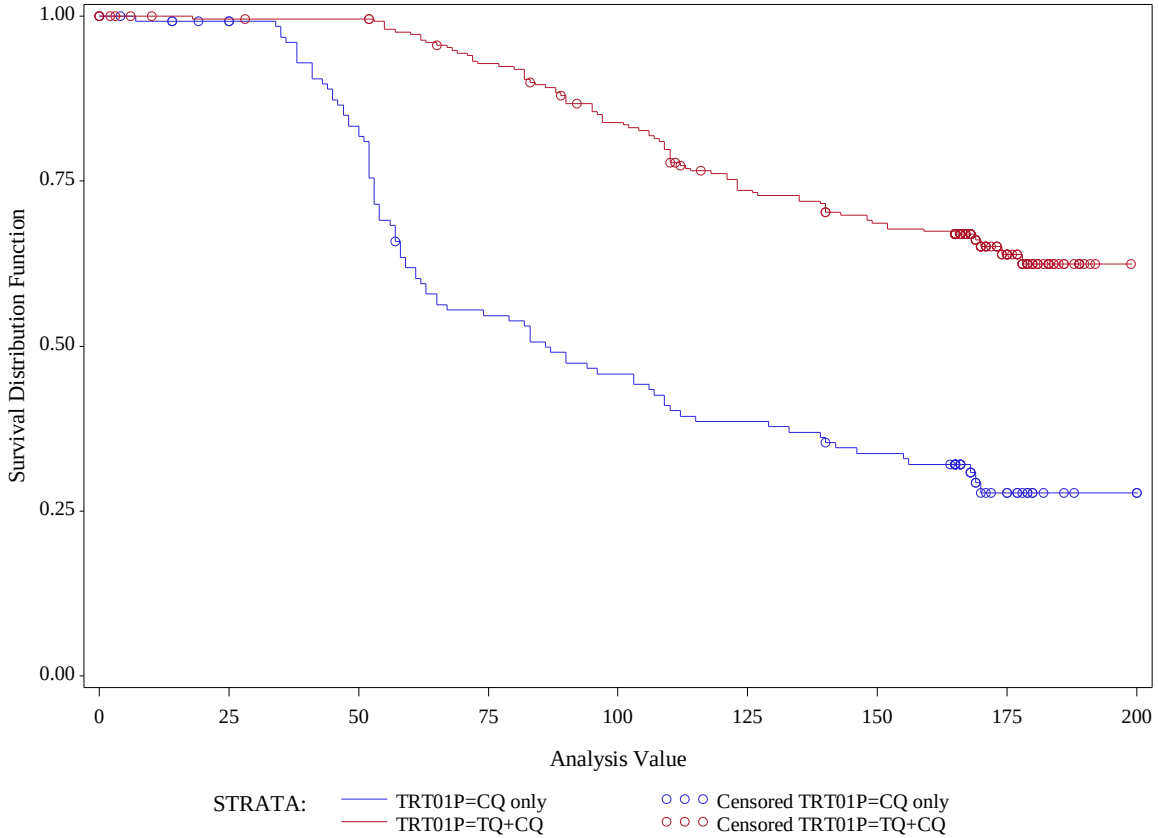
Study 582 Part 2: Baseline

	CQ Alone	CQ + TQ	CQ + PQ
Randomized	133	260	123
Micro-ITT	133	260	123
Male, n(%)	97 (73)	196 (75)	99 (77)
Age Mean (SD)	35.3 (14.2)	35.0 (14.4)	34.7 (14.3)
P. vivax - asexual parasite count/µL, median (range)	5615.0 (101, 66010)	5313.5 (112, 99604)	4380.0 (125, 87380)

Study 582 Part 2: 6-Month Results

	CQ Alone	CQ + TQ	CQ + PQ
Recurrence-free at 6 months, n(%)	35 (26)	155 (60)	83 (64)
Recurrence, n(%)	88 (66)	85 (33)	36 (28)
Censored, n(%)	10 (8)	20 (8)	10 (8)
Recurrence-free efficacy (%) up to 6 months			
Kaplan-Meier estimate (95% CI)	28 (20,36)	62 (55,69)	70 (60,77)
Difference in proportions (95% CI)		33(23, 43)	38 (27,49)
P-value from Log-rank test		<0.001	<0.001

Study 582 Part 2: 6-Month KM Curves



Study 582 Part 2: 6-Month Cox Regression Results

	CQ + TQ	CQ + PQ
Hazard ratio of risk of recurrence		
Estimate (95% CI)	0.30 (0.22,0.40)	0.26 (0.18,0.39)
P-value	<0.001	<0.001
Hazard ratio of risk of recurrence (Censoring=failure)		
Estimate (95% CI)	0.35 (0.26,0.46)	0.31 (0.22, 0.44)
P-value	<0.001	<0.001

Study 582 Part 2: 6-Month Subgroup Analyses

- Subgroup analyses showed consistent treatment results across age, gender, weight, race, region, and baseline parasite counts.

Study 582 Part 2: Early response

	CQ Alone (N=133)	CQ + TQ (N=260)	CQ + PQ (N=129)
Parasite clearance (PC), n(%)	129 (97)	254 (98)	127 (98)
Time to PC (hrs): Median (95%CI)	43 (41,48)	45 (42,47)	42 (39,45)
Fever clearance (FC), n(%)	48 (36)	102 (39)	47 (36)
Time to FC (hrs): Median (95%CI)	7 (5,14)	7 (5,12)	8 (6,18)
Gametocyte clearance (GC), n(%)	85 (64)	168 (65)	79 (61)
Time to GC (hrs): Median (95% CI)	38 (32,40)	39 (37,41)	36 (24,41)

Study 582 Part 2: 4-month Results

	CQ	CQ + TQ	CQ + PQ
Recurrence-free at 4 months, n(%)	47 (35)	177 (68)	90 (70)
Recurrence, n(%)	78 (59)	67 (26)	30 (23)
Censored, n(%)	8 (6)	16 (6)	9 (7)
Recurrence-free efficacy (%) up to 4 months			
Kaplan-Meier estimate (95% CI)	36 (27,45)	73 (20,38)	75 (66,82)
Hazard ratio of risk of recurrence (95% CI)		0.27 (0.20,0.38)	0.26 (0.17,0.39)
P-value from Log-rank test		<0.001	<0.001

Study 582 Part 2: Conclusion

- There was a statistically significant reduction in the risk of recurrence at 6 months in the CQ+TQ group compared with the CQ treatment alone.

Study 564: Study Design

- The primary objective was safety
- Conducted in Brazil, Columbia, Peru, Thailand, and Vietnam
- Active-controlled study
- Subjects randomized 2:1 to
  - CQ + TQ (300 mg, single dose)
  - CQ + PQ (14 days)
- CQ was given on Days 1 to 3

Study 564: Study Design

- Key Inclusion Criteria
  - Positive malaria smear for *P. vivax*
  - Parasite density between 100 and 100,000/uL
  - Appropriate G6PD level specified in the protocol
- Key Exclusion Criteria
  - Mixed malaria infection
  - Severe *P. vivax* malaria as defined by WHO criteria

Study 564: Efficacy Endpoint

- No primary efficacy endpoint was defined.
- FDA's analysis focused on the recurrence-free efficacy 6 months post-dosing (positive at baseline, initial clearance + not positive by Day 201).
  - Initial clearance: two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval.

Study 564: Analysis Methods

- Microbiologic ITT (micro-ITT): all randomized subjects who received at least 1 dose of study medication and had microscopically-confirmed *vivax* parasitemia
- Comparison of recurrence-free proportions

Study 564: Baseline

	CQ+TQ	CQ+PQ
Randomized	166	85
Micro-ITT	166	85
Male	114 (69)	53 (62)
Age Mean(SD)	37.5 (14.28)	37.7 (14.69)
P. vivax-asexual parasite count/uL median (range)	3617.5 (102, 45410)	5128.0 (104, 82650)

Study 564: 6-Month Results

	CQ+TQ (N=166)	CQ+PQ (N=85)
Recurrence-free efficacy, n(%)	112 (67)	60 (71)
Recurrence, n(%)	42 (25)	20 (24)
Censored, n(%)	12 (7)	5 (6)
Difference in recurrence-free efficacy (missing=failure, TQ-PQ) (%)		
Estimate (TQ-PQ) (95% CI)	-3.4 (-16, 9.8)	

Study 564: Conclusion

- This study supported the efficacy of TQ (300 mg single dose).

Conclusions

TQ 300 mg single dose efficacy evaluated in three clinical trials:

- Two trials using CQ alone as a control group demonstrated a statistically significant treatment effect for the proposed regimen for the radical cure of *P. vivax*.
- A trial using CQ+PQ group as the control group further supported the efficacy of the product.

NDA 210795: Tafenoquine for the radical cure of *Plasmodium vivax* malaria

Safety Review

Antimicrobial Drugs Advisory Committee Meeting

July 12, 2018

Elizabeth O'Shaughnessy, MB, BCh

Medical Officer, Division of Anti-Infective Products, FDA

Tafenoquine: Pharmacokinetic Highlights

Absorption	Distribution
• T_{max}: 12 -15 hours • Food (high-calorie, high-fat meal) increased TQ exposures (AUC↑43% and C_{max}↑31%)	• Highly protein bound (>99.5%) • Preferential RBC partitioning (67% higher drug level in whole blood than plasma)
Metabolism	**Elimination**
• Slow and negligible in vitro metabolism • No major metabolites in human	• $T_{1/2}$: ~ 15 days • Definitive excretion unknown; minor elimination in urine observed • PK has not been evaluated in subjects with renal or hepatic impairment
Drug-Drug Interaction	
• No clinically significant PK interactions between TQ and concomitantly used anti-malaria drugs (chloroquine, dihydroartemisinin-piperaquine, artemether-lumefantrine) • No clinically significant effect of TQ on the PK of substrates of CYPs 1A2, 2A6, 2C8, 2C9 and 3A4 • Tafenoquine inhibited human transporters OCT2 and MATE in vitro • The effect of TQ on the following transporters is not known: P-gp, BCRP, OATP1B1, OATP1B3	

Safety Review - Clinical Studies

- 3 double-blind, randomized trials of TQ single dose + CQ in patients with *P. vivax* malaria
  - Study 582, Part 1: TQ 50mg to 600mg (dose-ranging) + CQ
  - Study 582, Part 2: TQ 300mg + CQ
  - Study 564: TQ 300mg + CQ

- 3 studies in healthy subjects
  - Thorough QT; Ophthalmologic safety; Hemolytic potential of TQ.
  - TQ: 100mg up to 1,200mg (without CQ)

Phase 2b/3 Trials
Exposure to TQ 300mg single-dose

Clinical Trial	Number of Patients per Treatment Arm		
	TQ 300mg + CQ	PQ 15mg x 14d + CQ	CQ
Study 582, part 1	57	50	54
Study 582, part 2	260	129	133
Study 564	166	85	NA
Total no. patients	483	264	187

Phase 1 Studies

Phase 1 Study	G6PD Status	TQ Doses	No. of subjects exposed to TQ	Comparators (no. of subjects)	Total No. Subjects
Thorough QT	Normal	300, 600, 1200 mg	156	Placebo (52), Moxifloxacin (52)	260
027	Normal (24) Deficient (27)	100, 200, 300mg capsules	42	PQ 15mg x 14d (9)	51
Ophtho. Safety TQ	Normal	300mg	330	Placebo (168)	498

Outline of Safety Review

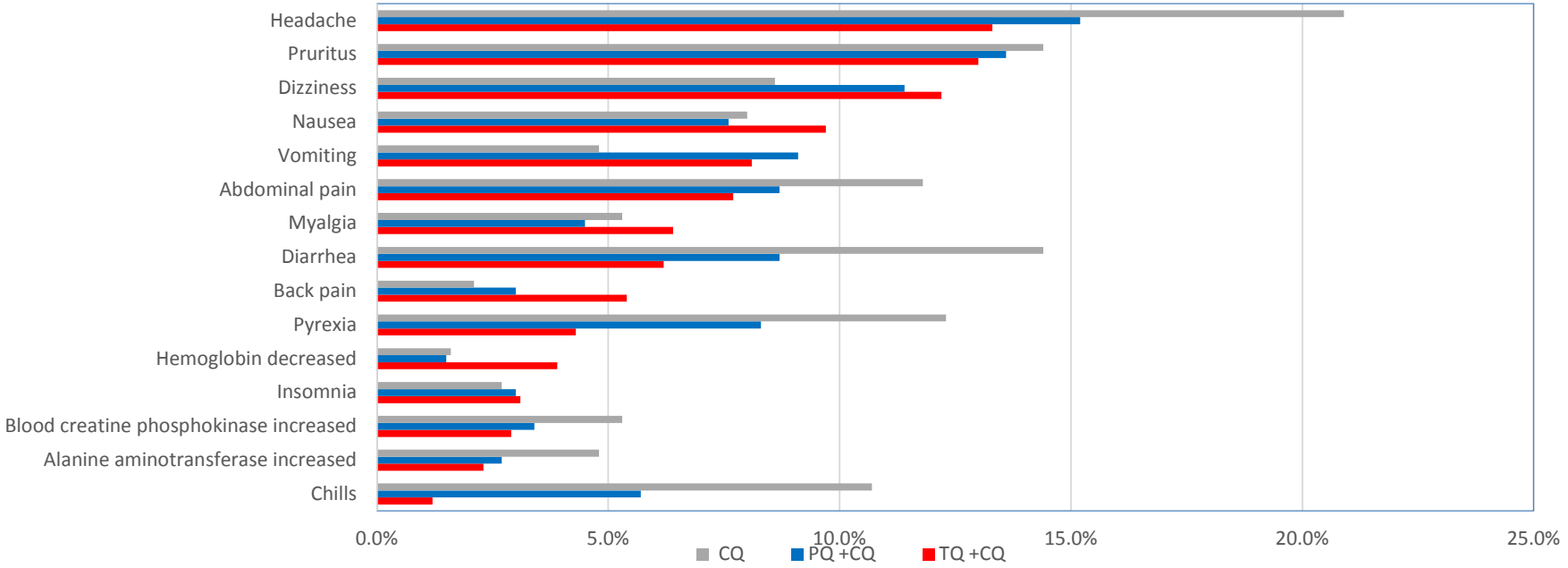
- Common adverse events
- Serious adverse events
- Adverse events of special interest associated with the 8-aminoquinoline, 4-aminoquinoline, and 4-quinoline-methanol antimalarials
  - Hematologic, Neurologic, Psychiatric, Cardiac, and Ophthalmologic

Study 582 (part 1 & 2) and 564
Overview of Adverse Events

Parameter	Study 582 part 1 & 2 and Study 564 : Treatment Arms		
	TQ 300mg + CQ N = 483	PQ + CQ N = 264	CQ N =187
AEs	321 (66%)	172 (65%)	127(68%)
SAEs	29 (6%)	12(5%)	10 (5%)
Deaths	0	0	0
AE – withdrawal from trial	0	0	0
AE – discontinuation of drugs	13 (3%)	2 (0.7%)	6 (3%)

Studies 582, Part 1 &2 and 564
Select Treatment Emergent Adverse Events

TEAE pooled treatment studies 582 part 1&2 and 564



Study 582 (part 1&2) and Study 564
Select Serious Adverse Events (SAE)

SAE	Study 582, part 1 &2 and Study 564: Treatment Arms		
	TQ 300mg + CQ N = 483	PQ+CQ N = 264	CQ N = 187
Hemoglobin decreased	18 (3.7%)	4(1.5%)	3(1.6%)
QT prolongation	1(0.2%)	4(1.5%)	5 (2.7%)
Drug-induced liver injury	1 (0.2%)	0	0

Studies 582 part 1&2 and 564
Hepatic Adverse Events

- Some patients presented with elevated transaminases and bilirubin levels at baseline associated with *P. vivax* malaria. Resolved with antimalarial treatment.
- Elevated transaminases post baseline were observed in the TQ 300mg +CQ group, for example in Study 582, part 2:
    - 2 patients developed elevated ALT (< 5x ULN) during first week of treatment which resolved.
    - 1 patient with an elevated ALT and bilirubin at baseline had an SAE of elevated transaminases - ALT elevation > 10x ULN. Patient recovered.
        - may have been related to ingestion of herbal medicines (ALT/AST declined when herbal meds stopped) but cannot rule out an effect of TQ+CQ.
        - Hepatic transaminases returned to baseline values.

Cardiac and Renal Adverse Events

- **Cardiac (Studies 582 part 1&2 and 564) :**
  - No clinically significant adverse events
  - < 5% of subjects in each of three treatment groups had a increase in QTcF > 60 ms and interval > 480 ms. Patients were asymptomatic.
- **Thorough QT Study:**
  - No evidence of QTcF prolongation for single doses TQ 300 mg and 600 mg.
  - TQ 1200 mg had maximum effect on QTcF within the safety margin of 10 ms - demonstrates lack of effect.
- **Renal (Studies 582 part 1&2 and 564) :**
  - Elevations in creatinine from baseline were mild and transient.

Healthy Volunteer Studies
Common and Serious Adverse Events

Thorough QT Study
Treatment Emergent Adverse Events

MedDRA preferred term	Placebo N=52	Moxifloxacin N=52	TQ 300mg N=52	TQ 600mg N=52	TQ 1200mg N=52
Nausea	2 (3.9%)	0	5 (9.6%)	8 (15.4%)	17 (32.7%)
Diarrhea	4 (7.7%)	1 (1.9%)	1 (1.9%)	10 (19.2)	5 (9.6%)
Headache	4 (7.7%)	2 (3.9%)	7 (13.5%)	6 (11.5%)	5 (9.6%)
Back pain	0	0	0	0	2 (3.9%)
Arthralgia	0	0	0	0	2 (3.9%)
Dizziness	0	3 (5.8%)	2 (3.9%)	2 (3.9%)	2 (3.9%)
Musculoskeletal pain	0	0	0	2 (3.9%)	1 (1.9%)
Somnolence	0	0	1 (1.9%)	1 (1.9%)	1 (1.9%)
Rash	1 (1.9%)	0	0	0	1 (1.9%)
Vomiting	0	1 (1.9%)	2 (3.9%)	4 (7.7%)	1 (1.9%)
Abdominal pain	0	1 (1.9%)	0	7 (13.5%)	1 (1.9%)
Aspartate aminotransferase incr.	0	0	0	2 (3.9%)	0
Urticaria	1 (1.9%)	0	1 (1.9%)	0	0
Blood creatine phosphokinase (CPK) increase	1 (1.9%)	0	0	2 (3.9%)	0
Pruritus	0	2 (3.9%)	1 (1.9%)	0	0

Thorough QT Study: Serious Adverse Events

MedDRA Preferred Term	Placebo N = 52	Moxifloxacin N = 52	TQ 300mg N = 52	TQ 600mg N = 52	TQ 1200mg N = 52
Hypersensitivity	0	0	0	**1 (1.9%)**	0
Blood CPK increased	1 (1.9%)	0	0	2 (3.9%)	0
Hemoglobin decreased	0	0	0	1 (1.9%)	0
Urticaria	0	0	**1 (1.9%)**	0	0

Study 027
Treatment Emergent Adverse Events

Dictionary-Derived Term	TQ 100 mg single dose N = 11	TQ 200 mg single dose N =12	TQ 300 mg single dose N = 19	PQ 15mg daily for 14 days N = 9
Hemoglobin decreased	4 (36.3%)	0	3 (15.8%)	2 (22.2%)
Hematocrit decreased	0	1 (8.3%)	0	1 (11.1%)
Dizziness	1 (9.0%)	1 (8.3%)	0	0
Headache	2 (18.2%)	0	0	0
Alanine aminotransferase increased	0	1 (8.3%)	0	0
Aspartate aminotransferase increased	0	1 (8.3%)	0	0
Pyrexia	1 (9%)	0	0	0
Nausea	1 (9%)	0	0	0
Myalgia	1 (9%)	0	0	0

Ophthalmologic Safety Study
Treatment Emergent Adverse Events

- No deaths or SAEs
- Headache (23 subjects, 7%) and nausea (14 subjects, 4%) were common in the TQ 300mg arm
- Dizziness, somnolence, and dysgeusia (2 subjects each, <1%) in the TQ group vs. none in placebo group
- No significant decreases in mean hemoglobin levels
- Small increases in methemoglobin %

Adverse Events of Special Interest

- Hematologic
- Neurologic
- Psychiatric
- Ophthalmologic

Study 582 and 564: Hematologic TEAEs

Dictionary Derived Term	TQ 300mg sd + CQ N = 483	CQ N = 187	PQ 15mg x 14d + CQ N =264
Anemia	1 (0.2%)	0	3 (1.1%)
Blood bilirubin increased	1 (0.2%)	NR	0
Dyspnea	2 (0.4%)	0	0
Fatigue	3 (0.6%)	2 (1.1%)	0
Hemoglobin decreased	**18 (3.7%)**	**3 (1.6%)**	**4 (1.5%)**
Hyperbilirubinemia	1 (0.2%)	1 (0.5%)	1 (0.4%)
Pallor	1 (0.2%)	0	0
Tachypnea	1 (0.2%)	0	0

Study 582 part 1:
Hemoglobin decrease from baseline Day 1 to 29

Hemoglobin (g/dL) decrease from baseline	TQ 50mg + CQ N=55	TQ 100mg + CQ N=57	TQ 300mg + CQ N=57	TQ 600mg + CQ N=56	PQ 15mg x 14d + CQ N=50	CQ N=54
> 1.5 to ≤ 2.5	7(13%)	19(33%)	17(30%)	22(39%)	15(30%)	15 (28%)
> 2.5g/dL or ≥ 25%	0	1(2%)	2(4%)	1(2%)	1(2%)	1(2%)

Study 582 part 2
Hemoglobin decrease from baseline Day 1 to 29

Hemoglobin (g/dL) decrease from baseline	TQ 300mg + CQ N=260	PQ 15mg x14d + CQ N=129	CQ N=133
> 2 to ≤ 3.0	31 (12%)	12 (9%)	11 (8%)
> 3g/dL or ≥ 30%	14 (5%)	3 (2%)	2 (2%)

Study 564
Hemoglobin decrease from baseline Day 1 to 29

Hemoglobin (g/dL) decrease from baseline	TQ 300mg +CQ N=166	PQ 15 mg x 14d + CQ N=85
> 2 to ≤ 3.0	32 (19%)	14 (16%)
> 3g/dL or ≥ 30%	4 (2%)	1 (1%)

Thorough QT Study
Hemoglobin decrease from baseline - Healthy subjects

Hemoglobin (g/dL) Decrease from baseline	Placebo N=52	Moxi N=52	TQ 300mg N=52	TQ 600mg N=52	TQ 1200mg N=52
>1 to ≤ 2	16 (31%)	18 (35%)	16 (31%)	19 (37%)	18 (35%)
>2 to ≤ 3	2 (4%)	3 (6%)	2 (4%)	4 (8%)	4 (8%)
> 3 g/dL	0	0	0	0	0

Study 027: Hemoglobin decrease from baseline

Hemoglobin (g/dL) - decrease from baseline	PQ 15mg x 14d	TQ 100mg	TQ 200mg	TQ 300mg
G6PD normal	**N = 6**	**N = 6**	**N = 6**	**N = 6**
>1.0 to ≤ 2.0	4(67%)	4(67%)	4(67%)	2(33%)
>2.0	0	0	1(17%)	0
G6PD deficient	**N = 5**	**N = 6**	**N = 13**	**N = 3**
> 1.0 to ≤ 2.0	1 (20%)	3 (50%)	9 (69%)	0
> 2.0 to ≤ 3.0	4 (80%)	2 (33%)	1 (8%)	3 (100%)
> 3.0	0	0	1 (8%)	0

Studies 582, part 1 & 2 and 564
Methemoglobin % Increase from Baseline

Phase 2b/3 Trials	Treatment Arms			MetHb% max. value	Signs and Symptoms
	TQ 300mg + CQ N=483	PQ + CQ N=264	CQ N=187		
582 part 1	0	1 (0.4%)	0	12.5%	Fatigue
582 part 2	5 (1%)	11 (4%)	4(2%)	13%	None reported
564	2 (0.4%)	3 (1.1%)	-	> 10%	None reported

Study 582 Part 1 and 2, and 564
Summary of Hematologic Findings

- Declines in hemoglobin (Hb) levels were not in the anemic range in most patients.
- Hb levels recovered without intervention such as blood transfusion.
- Declines in Hb observed in G6PD-normal patients
  - accompanied by reticulocytosis, no significant changes in haptoglobin and bilirubin
  - *P. vivax* malaria and rehydration may have contributed
- Elevations in methemoglobin % - asymptomatic; more frequent with PQ+CQ
- Low no. of G6PD-deficient patients with enzyme activity < 70%

Study 582 and 564: Neurologic Adverse Events

	Placebo (CQ) - controlled Trials: 582, Part 1 & 2, N=683			Primary Efficacy and Safety Trials: 582 part 1&2 and 564 N=747	
Dictionary Derived Term	TQ + CQ N = 317	CQ N = 187	PQ + CQ N =179	**TQ 300mg + CQ N = 483**	**PQ + CQ N = 264**
Balance disorder	-	-	-	1 (0.3%)	0
Dizziness	**30 (9.5%)**	**16 (8.6%)**	**14 (7.8%)**	**59 (12.2%)**	**30 (11.3%)**
Headache	**37 (11.7%)**	**39 (20.9%)**	**24 (13.4%)**	**64 (13.3%)**	**40 (15.2%)**
Migraine	3 (0.9%)	1 (0.5%)	0	3 (0.6%)	1 (0.4%)
Somnolence	1 (0.3%)	0	0	1 (0.2%)	0
Syncope	2 (0.6%)	0	1 (0.6%)	2 (0.4%)	1 (0.4%)
Tremor	1 (0.3%)	0	1(0.6%)	1 (0.2%)	1 (0.4%)

Study 582 and 564: Psychiatric TEAEs

	Placebo - controlled Trials: 582, Parts 1&2 N = 683			Primary Efficacy and Safety Trials: 582 parts 1&2 and 564 N = 747	
Dictionary Derived Term	TQ 300mg + CQ N = 317	CQ only N = 187	PQ + CQ N = 179	**TQ 300mg sd + CQ N = 483**	**PQ 15mg od + CQ N = 264**
Anxiety	2 (0.6%)	0	0	2 (0.4%)	3 (1.1%)
Depression	0	0	0	0	1 (0.3%)
Insomnia	13 (4.1%)	5 (2.7%)	8 (4.4%)	15 (3.1%)	8 (3.0%)

Psychiatric TEAEs in Clinical Program

- 2 cases of psychosis
  - 1 subject: TQ 350mg single-dose
    - pt. had previous episodes of psychosis
  - 1 subject: TQ 500mg single-dose
    - recent diagnosis of schizophrenia
  - Both patients were hospitalized and recovered.
- 2 cases depression/depressed mood post TQ 600mg.
  - 1 healthy subject developed depressed mood on study Day 4 – resolved without treatment in 3 days.
  - 1 patient (vivax malaria) with a history of depression/diazepam use was hospitalized for depression at Day 88 post TQ+CQ – discharged in 2 days and received psychiatric referral.

Ophthalmologic TEAEs

- Ophthalmologic TEAEs were infrequent across the treatment groups in clinical trials 582 part 1&2, and 564
- Ophthalmologic Safety Study
  - 330 patients exposed to TQ 300mg and 168 patients in placebo arm
  - No retinal toxicity or other ocular abnormality post TQ 300mg single dose.
  - Ophthalmology Consult: No significant ocular risk from the use of TQ 300mg single-dose.

Summary of Safety

- TQ 300mg + CQ was reasonably safe and well tolerated – dizziness, nausea, vomiting, headache, and decreases in hemoglobin
- Risk of hemolysis/ hemolytic anemia
  - Patients with G6PD < 70% activity. Test for G6PD deficiency.
- Hemoglobin decreases > 3g/dL from baseline occurred in some G6PD normal patients with vivax malaria.
- Methemoglobin % increase - more frequent in PQ+CQ in clinical trials. Patients were asymptomatic.

Summary of Safety cont.

- Caution is advised in patients with history of psychiatric disorder
- No retinal toxicity or other ocular abnormalities with TQ 300mg single dose
- No significant QTcF prolongation

U.S. FOOD & DRUG ADMINISTRATION

Backup Slides Shown

Nonclinical Pharmacology and Toxicology

Nonclinical Pharmacology Toxicology Program

- Pharmacology
  - Safety Pharmacology
- Pharmacokinetics
- Toxicology-
  - Single dose
  - Repeat dose (6 months rat, 12 months dog)
- Genotoxicity
- Carcinogenicity (2 years rat, mouse)
- Reproductive Toxicology
- Juvenile Toxicology

Adverse events of special interest

- Methemoglobinemia
- Mild anemia/Reticulocytosis
- Hemosiderin deposits
- Phospholipidosis (including foamy macrophages in lung)
- Increased renal tumors (male rat)
- Abortions (rabbit)

Evaluation of neurotoxic potential

- Single dose oral neurobehavioral assessment in adult rat
- Multiple dose oral juvenile toxicity study in the rat

Single dose oral neurobehavioral assessment in adult rat

- Rats (6/sex/group) were given a single oral gavage dose of tafenoquine
- Doses 125, 250 or 500 mg/kg
- Neurofunctional assessments

Single dose oral neurobehavioral assessment in adult rat

Timepoint	Observations
Day prior to dosing	FOB + Locomotor activity
30 mins. postdose	FOB
3 hours. postdose	FOB
6 hours postdose	Locomotor activity
24 hours postdose	Locomotor activity
48 hours postdose	Locomotor activity

Functional Observational Battery

grip strength	landing foot splay	stereotypy
posture	reactivity to handling	gait
eyelid closure	chromodacryorrhea	pupil response
vocalization	convulsions	ease of locomotion
air righting	salivation	arousal
ease of removal	tremors	piloerection
exophthalmia	response to visual approach	auditory assessments
pinna reflex	proprioception	pain perception
fasciculation	body temperature	Condition of coat
unformed feces	Number of fecal pellets	Number of pools of urine

Motor Activity

- The locomotor activity of all neurobehavioral animals was measured during a 60 minute session
- Session composed of 12 5-minute intervals using an automated motor monitor system.
- The total number of horizontal and vertical movements that occurred during each of the 5-minute intervals was recorded.
- Following oral administration of Tafenoquine, no drug-related adverse findings.
- Lowest dose estimated at 13 fold human dose based on C_{max} comparisons

Oral juvenile toxicity study in the rat

- Juvenile rats (dosed PND 7-62)
- Tafenoquine doses 0 (vehicle), 5, 15 or 25 mg/kg orally every five days
- Dose increased to 0 (vehicle) 10, 20 or 50 mg/kg every five days
- Two weeks after last dose neurobehavioral evaluations to assess latent effects of dosing on behavior.
- Motor activity, pre-pulse inhibition of auditory startle response and learning and memory ability (Morris water maze)
- No drug-related effects on neurobehavioral function
- Lowest dose estimated at 7-fold human dose based on C_{max} comparisons.

Overall conclusion

- Tafenoquine was not associated with any drug-related adverse neurobehavioral or histopathology findings in either study