World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

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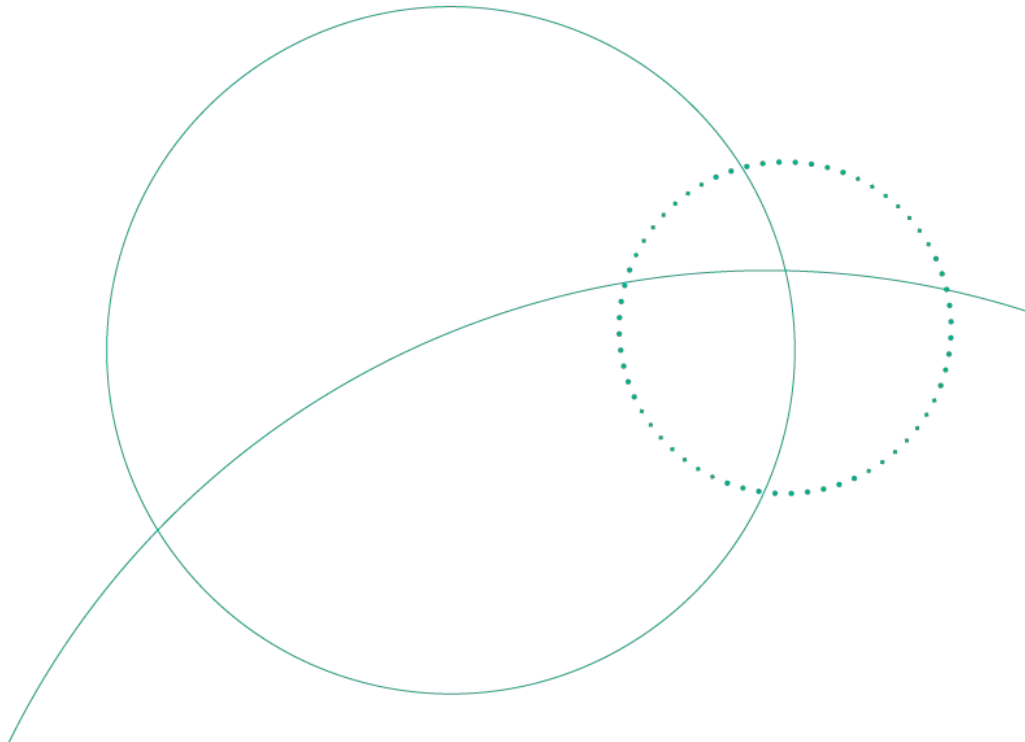
Yorkool G5 LN

(Tianjin Yorkool International Trading Co., Ltd)

P-12507

Efficacy Assessment



Contents

1 Introduction

The primary purpose for the use of a pesticide is the control of a pest, including disease transmitting vectors. Vector control tools, including formulated pesticides, which provide effective management or control of vectors, may be used as part of a resistance management programme. Vector control products for use in public health are a component of Integrated Vector Management (IVM), which is a programme that relies on a suite of diverse interventions and implementations of best practices to manage the vector and chemical/behavioural resistance.

Yorkool G5 is a homogenous ITN coated with 2.4 g AI/kg alpha-cypermethrin and 4.8 g AI/kg chlorfenapyr that is intended to provide personal and community protection from Anopheline mosquitoes as part of malaria control programmes.

Semi-field studies to characterize the performance of Yorkool G5 against free-flying mosquitoes with supplementary bioassays to characterize the availability of active ingredients and insecticidal effect of the fabric of the ITN on Anopheline mosquito species were submitted to WHO as part of the prequalification dossier.

2 Semi-field studies

Studies conducted in semi-field settings often include the investigation of endpoints other than mortality, knockdown and blood-feeding inhibition. Examples of these include entry rate, exit rate, and deterrence, as well as analyses for non-standardized calculations of “personal protection”. Based on the existing requirements and established decision framework, mosquito mortality and knockdown are considered the primary endpoints for assessment. Therefore, results for these are included within the summaries of these studies. Calculations of blood feeding inhibition were also included for further characterization of the entomological impact of the product.

2.1 Semi-field studies

Data on the semi-field performance of Yorkool G5 were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP). These summary results are based on ITNs drawn from batches 20211013, 20211108 and 20211203.

Two semi-field studies were presented to evaluate the efficacy and wash resistance of Yorkool G5 in Benin and Tanzania. Both semi-field studies that were conducted were experimental hut trials (EHTs). ITNs used in semi-field studies were prepared using a wash interval of five days that was selected based on the results from the Module 3 laboratory studies. The endpoint used to evaluate bioavailability was 72-hour mortality. The negative control used in each study was an untreated net. The positive controls used in the semi-field studies were a prequalified ITN product treated with 2.4 g AI/kg alpha-cypermethrin and 4.8 g AI/kg chlorfenapyr, hereafter referred to as PC1, a prequalified ITN product treated with 5.0 g AI/kg alpha-cypermethrin, hereafter referred to as PC2, and a prequalified ITN product treated with 4.5 g AI/kg alpha-cypermethrin, hereafter referred to as PC3. In non-inferiority analyses conducted on the results of the semi-field studies, PC1 was used as an active comparator; PC2 and PC3 were used as standard comparators.

The product was tested against pyrethroid resistant natural populations of, in Covè, Benin, *An. coluzzi* and *An. gambiae* s.s, with the relative proportions estimated at 77% and 23%, respectively. The pyrethroid resistance is mediated by *kdr,* with the *An. gambiae* s.l population carrying *kdr* gene frequencies of >90% L1014F and an intensity of resistance of greater than 200-fold the diagnostic dose, and metabolic resistance through over-expression of CYP6P3 enzymes. In resistance testing conducted during the EHT, 16% and 98% mortality were observed following exposure to the diagnostic doses of alpha-cypermethrin and chlorfenapyr, respectively. In resistance intensity testing conducted using 10x the diagnostic dose of alpha-cypermethrin, 40% mortality was observed.

In the semi-field study conducted in Tanzania, the product was tested against pyrethroid resistant natural populations of the *An. gambiae* complex, of which >99.9% was *An. arabiensis*. In resistance testing conducted prior to the EHT, 13% mortality was observed following exposure to the diagnostic dose of alpha-cypermethrin. Resistance testing using the diagnostic dose of chlorfenapyr was not conducted.

The results from the free-flying mosquito studies are presented in Table 1. Yorkool G5 ITNs that were washed 20 times using a 5-day wash interval induced 50.3% 72-hour mortality in wild free-flying *An. gambiae* s.l. mosquitoes in Benin and 34.6% 72-hour mortality in free-flying *An. arabiensis* mosquitoes in Tanzania, respectively. Non-inferiority statistical analyses demonstrated that, following 20 washes using a five-day wash interval, Yorkool G5 was non-inferior to PC1 and superior to PC2 and PC3 for the mortality endpoint in both semi-field study locations (Table 2).

Supplementary bioassays were used to characterize the bioavailability of the active ingredients on the surface of the ITN pre- and post-hut studies using unwashed and 20x washed nets. WHO cone tests and tunnel tests were the experimental methods used in bioavailability studies. In Benin, tunnel tests using the insecticide susceptible *An. gambiae* s.s. Kisumu test system and the pyrethroid resistant *An. gambiae* s.l. Covè test system were used to evaluate bioavailability. In Tanzania, WHO cone tests and tunnel tests were conducted using the insecticide susceptible *An. gambiae* Ifakara test system (cone tests) and the pyrethroid resistant *An. arabiensis* Kingani test system (tunnel tests) for bioavailability evaluations. Thresholds of ≥95% knockdown and/or ≥80% mortality in WHO cone tests and ≥80% mortality or ≥90% blood feeding inhibition in tunnel tests were used as the efficacy criteria for bioavailability. The endpoint used to evaluate bioavailability was 72-hour mortality.

The results from supplementary bioassays are presented in Table 3. In tunnel tests conducted using insecticide susceptible and pyrethroid resistant test systems, greater than 80% mortality was observed at 72 hours post-exposure using unwashed and 20x washed nets, before and after the EHT in Benin. In Tanzania, greater than 80% mortality in tunnel tests conducted using a pyrethroid resistant test system was observed in tests conducted using unwashed nets before and after the EHT. The observed mortality in 20x washed nets was 33.8% before the EHT and 72.7% after the EHT. The increase in the observed mortality for 20x washed nets between the start and the end of the EHT in Tanzania may indicate that later in the life of the product, a wash interval longer than five days is required for full bioavailability of the AI on the surface of the fabric.

Table 1. Mortality and Blood Feeding Inhibition of Wild, Free-Flying Pyrethroid Resistant *An. gambiae* s.l. and *An. arabiensis* in Experimental Hut Trials in Benin and Tanzania				
Product	**Washing condition**	**% M72 (95% CI)**	**% Feeding inhibition (95% CI)**	**Sample Size**
Benin (*An.gambiae* s.l)				
Total number of mosquitoes collected = 6,761			Compliant with power calculation? Yes	
Control	Unwashed	0.7 (0.2 – 1.2)	-	1,187
Yorkool G5	Unwashed	59.3 (55.4 – 63.2)	33.3 (29.6 – 37.0)	612
	20x washed	50.3 (47.5 – 53.1)	18.2 (16.0 – 20.4)	1,217
PC1	Unwashed	60.6 (56.6 – 64.6)	32.0 (28.1 – 35.7)	581
	20x washed	48.8 (45.7 – 51.9)	18.7 (16.3 – 21.1)	1,026
PC2	Unwashed	15.3 (12.8 – 17.8)	24.9 (21.9 – 27.9)	780
	20x washed	12.2 (10.5 – 13.9)	6.7 (5.4 – 8.0)	1,358
Tanzania (*An.arabiensis*)				
Total number of mosquitoes collected = 22,100			Compliant with power calculation? Yes	
Control	Unwashed	0.7	-	4,461
Yorkool G5	Unwashed*	41.9 (38.1 – 45.7)	96.4 (95.1 – 97.7)	1,516
	20x washed*	34.6 (31.8 – 37.4)	95.2 (94.0 – 96.4)	3,323
PC1	Unwashed*	43.4 (39.4 – 47.4)	97.2 (95.9 – 98.4)	1,095
	20x washed*	34.5 (31.6 – 37.4)	95.8 (94.3 – 97.4)	2,790
PC3	Unwashed*	27.6 (24.4 – 30.8)	96.8 (96.0 – 97.7)	4,501
	20x washed*	27.3 (24.6 – 29.9)	96.5 (95.5 – 97.5)	4,414

* Control-corrected mortality

Table 2. Non-inferiority analysis for Yorkool G5 in experimental huts using wild, pyrethroid-resistant *Anopheles gambiae* s.l. mosquitoes in Covè, Southern Benin and wild, pyrethroid resistant *An. arabiensis* mosquitoes in Lupiro, Tanzania

	Unwashed					20x washed					Pooled				
Indicator and reference	Target Outcome	Non-inferiority margin	OR (95% CI)	p	Interpretation	Target Outcome	Non-inferiority margin	OR (95% CI)	p	Interpretation	Target Outcome	Non-inferiority margin	OR (95% CI)	p	Interpretation
Benin															
M72 PC1 (active comparator)	Non-inferiority	0.751	0.93 (**0.71**-1.20)	NA	Not non-inferior	Non-inferiority	0.753	1.02 (**0.84**-1.23)	NA	Non-inferior	Non-inferiority	0.755	0.983 (**0.84**-1.15)	NA	Non-inferior
M72 PC2 (standard comparator)	Superiority	NA	10.92 (8.20 – 14.53)	<0.001	Superior [a]	Superiority	NA	8.93 (7.12 – 11.18)	<0.001	Superior	Superiority	NA	9.75 (8.14-11.68)	<0.001	Superior
Blood feeding rate PC1 (active comparator)	Non-inferiority	1.328	1.09 (0.84-**1.40**)	NA	Not non-inferior	Non-inferiority	1.325	1.06 (0.88-**1.28**)	NA	Non-inferior	Non-inferiority	1.324	1.08 (0.93-**1.26**)	NA	Non-inferior
Blood feeding rate PC2 (standard comparator)	Superiority	NA	0.81 (0.64 – 1.03)	0.087	Not superior	Superiority	NA	0.70 (0.59 – 0.84)	<0.001 [a]	Superior	Superiority	NA	0.74 (0.64 - 0.85)	<0.001	Superior
Tanzania															
M72 PC1 (active comparator)	Non-inferiority	0.75	0.98 (**0.83**, 1.16)	NA	Non-inferior	Non-inferiority	0.73	1.01 (**0.90**, 1.13)	NA	Non-inferior	Non-inferiority	0.74	1.01 (**0.92**, 1.11)	NA	Non-inferior
M72 PC3 (standard comparator)	Superiority	NA	2.03 (1.79, 2.30)	<0.0001	Superior	Superiority	NA	1.54 (1.38, 1.71)	<0.0001	-	Superiority	NA	1.73 (1.60, 1.88)	<0.0001	Superior
Blood feeding rate PC1 (active comparator)	Non-inferiority	3.59	1.21 (0.76, **1.94**)	NA	Non-inferior	Non-inferiority	2.97	1.34 (1.03, **1.75**)	NA	Non-inferior	Non-inferiority	2.97	1.30 (1.03, **1.63**)	NA	Non-inferior
Blood feeding rate PC3 (standard comparator)	Superiority	NA	1.12 (0.80, 1.56)	0.523	Not superior	Superiority	NA	1.55 (1.22, 1.98)	<0.0001	Inferior	Superiority	NA	1.38 (1.14, 1.67)	0.001	Inferior

NA = Not applicable, NR = Not reported, non-inferiority margin representing a 7% difference in proportion,

WHO Prequalification of Vector Control Products
Avenue Appia 20
1211 Geneva 27
Switzerland

For further information, contact:
pqvectorcontrol@who.int
https://extranet.who.int/prequal/vector-control-products

Table 3. Knockdown, mortality and blood feeding inhibition results for insecticide susceptible and pyrethroid resistant laboratory strains using WHO cone bioassays and tunnel tests

	Benin			**Benin**		
	An. gambiae Kisumu			*An. gambiae* Covè		
	n	%M72 (95% CI)	%BFI (95% CI)	n	%M72 (95% CI)	%BFI (95% CI)
Before hut trial						
UW	196	100.0 (96 - 100)	97.8 (95.8 – 99.9)	217	96 (93 – 99)	94.2 (91.1 – 97.3)
20x washed	206	98.5 (97 - 100)	92.3 (88.7 – 95.9)	197	93 (89 – 96)	72.3 (66.1 – 78.6)
After hut trial						
UW	210	99.0 (98 – 100)	98.5 (96.9 – 100)	208	98 (96 – 99)	91.7 (87.9 – 95.5)
20x washed	205	97.6 (95 – 100)	95.9 (93.2 – 98.6)	189	98 (96 - 100)	87 (83 – 92.4)
	Tanzania			**Tanzania**		
	An. gambiae Ifakara			*An. arabiensis* Kingani		
	n	%KD60 (95% CI)	%M72 (95% CI)	n	%M72 (95% CI)	%BFI (95% CI)
Before hut trial						
UW	300	100	55.7 (49.0 – 62.3)	300	94.4 (84.2 – 100)	99.3 (97.7 – 100)
20x washed	300	100	43.6 (38.2 – 49.0)	298	33.8 (24.7 – 42.8)	97.0 (92.9 – 100)
After hut trial						
UW	200	100	51.0 (41.3 – 60.7)	197	88.6 (76.6 – 100)	100
20x washed	200	100	38.0 (31.1 – 44.9)	196	72.7 (64.1 – 81.4)	100

2.2 Chemical characterization

Data on the alpha-cypermethrin and chlorfenapyr content of sampled pieces of the Yorkool G5 LN product used in the semi-field studies were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP). These summary results are based on ITNs drawn from batches 20211013, 20211108 and 20211203. The results are summarized in Table 4.

Table 4. AI content and retention of sampled pieces of Yorkool G5 used in the semi-field studies in Benin and Tanzania (batch numbers 20211013, 20211108 and 20211203 - used in both locations)

	Benin				Tanzania			
	Mean alpha-cypermethrin content (g/kg)	Alpha-cypermethrin retention (per wash)	Mean chlorfenapyr content (g/kg)	Chlorfenapyr retention (per wash)	Mean alpha-cypermethrin content (g/kg)	Alpha-cypermethrin retention (per wash)	Mean chlorfenapyr content (g/kg)	Chlorfenapyr retention (per wash)
Before hut trial								
UW	2.40	-	4.00	-	2.43	-	4.16	-
20x washed	1.40	58.33% (97.34%)	2.10	52.50% (96.83%)	1.19	48.97% (96.49%)	2.45	58.89% (97.39%)
After hut trial					**After hut trial**			
UW	2.00	-	3.60	-	2.38	-	3.78	-
20x washed	1.4	70.00% (98.23%)	2	55.56% (97.10%)	1.25	52.52% (96.83%)	2.28	60.32% (97.50%)

For Tanzania, the mean AI content presented in Table 4 was determined based on 15 net samples for unwashed (UW) product and after 20 washes before hut trial and 10 net samples for unwashed (UW) product and after 20 washes after hut trial, all belonging to 3 batches (20211013, 20211108 and 20211203).

For Benin, the mean AI content presented in Table 4 was determined based on 5 net samples belonging to 3 batches (20211013, 20211108 and 20211203) for unwashed (UW) product and after 20 washes before hut trial and after hut trial.

AI retention per wash in Table 4 is calculated as:

- AI retention per wash = 100 x $\sqrt[n]{(t_n/t_0)}$ where:
  - t_n = total active ingredient content after n washing cycles
  - t_0 = total active ingredient content before washing
  - n = number of washes.

The chemical analysis performed on samples of ITNs used in the semi-field studies confirmed that the test samples conformed with the batch analysis data presented in Module 3 and that the test samples were appropriate for use in the study.

The AI content for the unwashed product complied with the target dose interval limits in the specification (i.e., 2.4 g/kg + 25% - 15% for alpha-cypermethrin, 4.8 ± 25% g/kg for chlorfenapyr).

2.3 Semi-field studies conclusions

The submitted semi-field studies demonstrate the impact of Yorkool G5 LN on free-flying mosquitoes and the bioavailability of the treatments on the ITN fabric using WHO cone bioassays and tunnel tests. Based on the submitted studies, the impact of Yorkool G5 LN ITNs that have been prepared using a 5-day wash interval can be sustained against pyrethroid resistant and insecticide susceptible free-flying mosquitoes up to 20 washes. The bioavailability of the treatments on the Yorkool G5 LN fabric was sustained up to 20 washes against insecticide susceptible test systems of the *An. gambiae* and *An. arabiensis*.

3 Efficacy conclusions

Based on the studies and information provided, all data requirements for the prequalification assessment of product efficacy have been satisfied. These data have been relied upon to assess the bioavailability and the impact on free-flying mosquitoes of the proposed product for the purpose of characterising the fabric of the product and establishing the duration of biological impact using products prepared with a defined wash interval.

The efficacy component of the dossier is considered complete, and the assessment of the submitted information on efficacy supports prequalification of the product.

Table 5. List of efficacy studies submitted to WHO as part of the prequalification dossier

Studies that were relied upon for decision making	
Study number	Study title
22-04	Experimental hut evaluation of the efficacy and wash resistance of Yorkool® G5 (a new alphacypermethrin and chlorfenapyr mixture bed nets by Tianjin Yorkool International Trading Co., Ltd) against wild, pyrethroid-resistant *Anopheles gambiae* sl in Covè, Southern Benin
BIT080 WP2	The non-inferiority evaluation of Yorkool G5 Insecticide treated nets in comparison to Interceptor G2 and MiraNet in the experimental huts against wild mosquitoes in Tanzania.
TE2023-032	Chemical analysis of Yorkool G5 LN IHI Phase 2 experimental hut study
TE2023-004	Chemical analysis of Yorkool G5 LN experimental hut study
Studies that were not used to inform decision making	
	None