World Health Organization

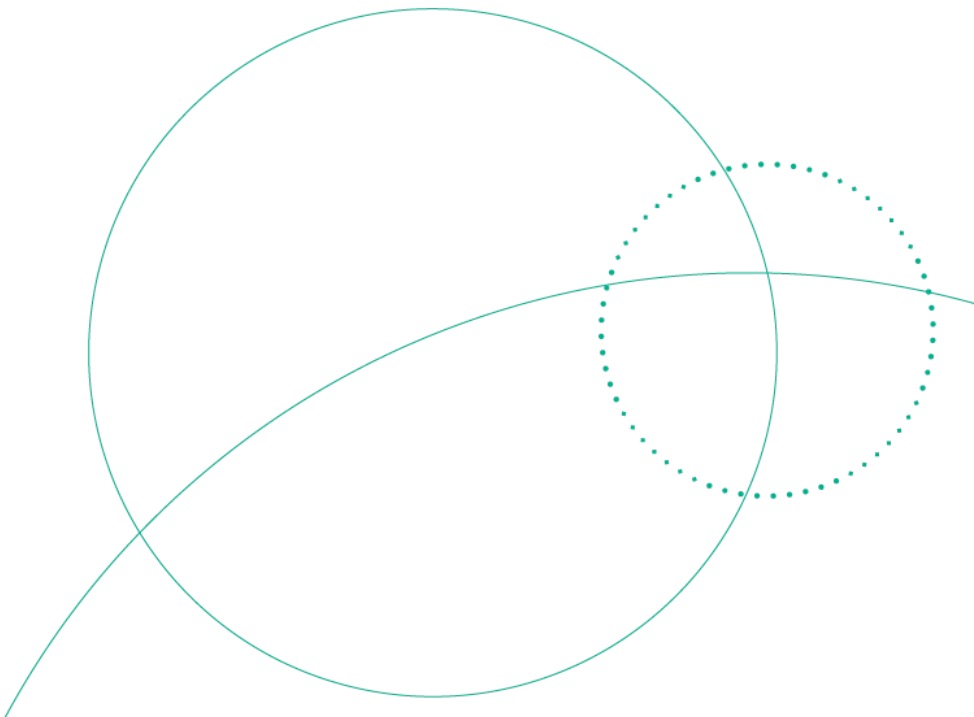
WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 5

SOVRENTA 15WP
(Syngenta Crop Protection AG)

P-11568

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.

SOVRENTA 15WP is a wettable powder formulation containing 150 g/kg (equivalent to 15% w/w) of isocycloseram that is intended to be used for the control of Anopheline mosquitoes as an indoor residual spray. The insecticidal mode of action on mosquitoes is through isocycloseram acting as an inhibitor of the GABA (gamma-amino butyric acid)-activated chloride channel at an allosteric site.

Semi-field studies to characterize the performance of SOVRENTA 15WP and the residual efficacy on wall surfaces in experimental huts were submitted to WHO as part of the prequalification dossier.

2 Semi-field studies

Studies conducted in the semi-field setting often include the investigation of endpoints other than mortality 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 is considered the primary endpoint for assessment. Therefore, results for these are included within the summaries of these studies. Calculations of blood feeding inhibition or results for blood feeding rate were also included for further characterization of the entomological impact of the product.

2.1 Experimental hut trials

Data on the semi-field performance of SOVRENTA 15WP and the residual efficacy on concrete/cement, mud wall surfaces and tarpaulin ceiling surfaces were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP). These summary results are drawn from product batch GP211015.

Two primary evidence semi-field studies and one supplementary evidence semi-field study were presented to evaluate the efficacy and residual activity of SOVRENTA 15WP. All three studies were conducted as experimental hut trials (EHT). The wall surfaces used in huts were mud and concrete/cement. In the supplementary evidence study, sprayed tarpaulin ceiling surfaces were tested in addition to wall surfaces. SOVRENTA 15WP was applied at 120 mg AI/m^2 and the endpoint used to evaluate bioavailability was 168-hour mortality.

In the primary evidence studies, conducted in Tanzania and Benin, one study used cattle as bait (Tanzania), and one study used human volunteers (Benin). The supplementary evidence study, conducted in Ghana, used human volunteers as bait. The negative control/s used in all three studies were water sprayed hut(s). The positive controls used in studies were prequalified products containing i) 300 g/L micro-encapsulated pirimiphos-methyl applied at 1,000 mg AI/m^2, hereafter referred to as PC1, and ii) 50% w/w of clothianidin applied at 300 mg AI/m^2, hereafter referred to as PC2. In non-

inferiority analyses conducted on the results of the semi-field studies, both PC1 and PC2 were used as comparators.

The duration of the EHTs were 12 months in Tanzania and Benin, and 13 months in Ghana. The product was tested against natural populations of: i) pyrethroid resistant *An. arabiensis* in Lupiro, Tanzania, carrying metabolic resistance due to upregulation of CYP450; ii) pyrethroid resistant *An. gambiae* s.l. in Covè, Benin, carrying *kdr* gene frequencies of >90% L1014F and metabolic resistance through over-expression of CYP6P3, and iii) pyrethroid resistant *An. gambiae* s.l. in Kulaa, Ghana, carrying metabolic resistance, and high frequencies of *kdr* and *ace-1* genes.

The results from the free-flying mosquito studies are presented in Table 1. Over 12 months, SOVRENTA 15WP induced an average of 86% mortality on the two tested wall surfaces in Tanzania. In Benin, the average mortality over 12 months was 72% in cement huts and 60% in mud huts, respectively, and in Ghana the average mortality over 13 months was 65% on the two tested surfaces. Non-inferiority analyses conducted in all three sites indicated that SOVRENTA 15WP was superior to PC1 and PC2 at three- and 12-months post-application in Tanzania and at 12 months post-application in Benin. In Ghana, the product was not non-inferior to PC2 on mud walls, and non-inferior to PC2 on cement walls at 13 months post-application (Table 2).

Supplementary bioassays using WHO cone tests were used to characterize the bioavailability of the active ingredients on the wall surfaces of the treated huts. Supplementary bioassays were carried out for 12 months in Tanzania and Benin and 13 months in Ghana. In Tanzania, the test systems used were insecticide-susceptible *An. gambiae* s.s. (Ifakara strain) and pyrethroid-resistant *An. arabiensis* (Kingani strain). In Benin, insecticide-susceptible *An. gambiae* (Kisumu strain) and pyrethroid-resistant *An. gambiae* s.l. (Covè strain) were used as test systems. In Ghana, *An. gambiae* s.s (Kisumu strain) was used as an insecticide susceptible test system; two pyrethroid resistant test systems were used: wild *An. gambiae* s.l. from the Kulaa study site, and colonised *An. gambiae* (Tiassalé strain).

The results from supplementary bioassays are presented in Table 3. In all sites and substrates, mortality greater than 80% was observed to 12 months post-application in both insecticide susceptible and pyrethroid resistant test systems.

Table 1. Mortality and blood feeding of free-flying wild pyrethroid resistant *Anopheles spp.* mosquitoes in experimental hut studies in Tanzania (12 months), Benin (12 months), and Ghana (13 months) using SOVRENTA 15WP applied at 120 mg AI/m².

Product	Hut surface	Treatment concentration (mg AI/m²)	% M24 (95% CI)	%M168* (95% CI)	%BFI† (95% CI)	Sample size
Tanzania (*An.arabiensis*)						
Total number of mosquitoes collected = 341,615‡			Compliant with power calculation? Yes			
Control	Concrete	N/A	0	1 (1-2)		43,695
	Mud	N/A	0	1 (1-2)		41,018
	Combined	N/A	0	1 (1-2)		84,713
SOVRENTA 15WP	Concrete	120	60 (57 – 63)	88 (86 – 89)	12 (10 – 15)	36,204
	Mud	120	55 (52 – 58)	84 (82 – 86)	13 (11 – 15)	32,824
	Combined	120	57 (55 – 60)	86 (84 – 87)	13 (11 - 14)	69,028
PC1	Concrete	1,000	15 (14 – 17)	58 (56 – 60)	15 (13 – 18)	37,199
	Mud	1,000	14 (12 – 15)	60 (57 – 62)	15 (13 – 18)	32,787
	Combined	1,000	15 (13 – 16)	59 (57 – 60)	14 (12 – 15)	69,986
PC2	Concrete	300	41 (39 – 44)	79 (77 – 81)	14 (12 – 17)	32,727
	Mud	300	36 (34 - 38)	75 (73 – 77)	13 (11 – 15)	31,412
	Combined	300	39 (37 – 40)	77 (75 – 78)	14 (12 – 15)	64,139
Benin (*An. gambiae* s.l.)						
Total number of mosquitoes collected = 19,267‡			Compliant with power calculation? No power calculation provided			
Control	Cement	N/A	1 (0 – 1)	1 (0 - 1)	99 (95 – 100)	2,532
SOVRENTA 15WP	Cement	120	42 (41 – 44)	72 (71 – 73)	99 (95 – 100)	4,085
	Mud	120	25 (23 – 27)	60 (58 – 62)	99 (95 – 100)	2,796
PC1	Cement	1,000	34 (32 – 36)	47 (45 – 50)	99 (95 – 100)	1,678
	Mud	1,000	32 (30 – 35)	44 (42 – 47)	99 (95 – 100)	1,759
Ghana (*An. gambiae* s.l)						
Total number of mosquitoes collected = 2,652‡			Compliant with power calculation? Yes			
Control	Cement	N/A	-	14.3 (10.1 – 19.4)	56.7 (50.2 – 63.1)	238
	Mud	N/A	-	18.1 (13.1 – 24.1)	56.9 (49.8 – 63.8)	204

Table 1. Mortality and blood feeding of free-flying wild pyrethroid resistant *Anopheles spp.* mosquitoes in experimental hut studies in Tanzania (12 months), Benin (12 months), and Ghana (13 months) using SOVRENTA 15WP applied at 120 mg AI/m².

Product	Hut surface	Treatment concentration (mg AI/m²)	% M24 (95% CI)	%M168* (95% CI)	%BFI† (95% CI)	Sample size
	Combined	N/A	-	16.1 (12.8 – 19.8)	-	442
SOVRENTA 15WP	Cement	120	-	61.0 (56.3 – 65.6)	51.3 (46.5 – 56.0)	439
	Mud	120	-	70.2 (65.1 – 75.0)	59.3 (54.0 – 64.5)	349
	Combined	120	-	65.1 (61.7 – 68.4)	-	788
PC2	Cement	300	-	71.4 (63.8 – 78.3)	55.9 (47.9 – 63.7)	161
	Mud	300	-	68.5 (62.8 – 73.8)	62.7 (56.8 – 68.2)	292
	Combined	300	-	69.5 (65.1 – 73.7)	-	453

* M72 in Ghana; †Blood feeding rate in Benin, Ghana; ‡Total number of mosquitoes collected may include additional study arms that are not reported in this document.

Table 2. Non-inferiority analyses for SOVRENTA 15WP in experimental hut studies in Tanzania, Benin and Ghana.

Indicator and reference	Mud				Concrete/Cement				Pooled			
	Target outcome	NI margin	OR (95% CI)	Interpretation	Target outcome	NI margin	OR (95% CI)	Interpretation	Target outcome	NI margin	OR (95% CI)	Interpretation
Tanzania												
M168 PC1 3 months	Non-inferiority	0.70	4.53 (3.37 – 6.07)	Superior	Non-inferiority	0.76	8.56 (6.31 – 11.63)	Superior	Non-inferiority	0.75	6.70 (5.50 – 8.15)	Superior
M168 PC1 12 months	Non-inferiority	0.75	3.50 (3.37 – 3.64)	Superior	Non-inferiority	0.75	3.38 (3.25 – 3.51)	Superior	Non-inferiority	0.75	3.45 (3.36 – 3.54)	Superior
M168 PC2 3 months	Non-inferiority	0.74	1.71 (1.28 – 2.28)	Superior	Non-inferiority	0.76	1.81 (1.29 – 2.54)	Superior	Non-inferiority	0.75	1.78 (1.44 – 2.21)	Superior
M168 PC2 12 months	Non-inferiority	0.72	1.90 (1.83 – 1.98)	Superior	Non-inferiority	0.70	1.44 (1.38 – 1.50)	Superior	Non-inferiority	0.71	1.68 (1.63 – 1.73)	Superior
Blood feeding rate PC1 3 months	Non-inferiority	1.51	0.69 (0.53 – 0.90)	Non-inferior	Non-inferiority	1.37	1.53 (1.20 – 1.94)	Not non-inferior	Non-inferiority	1.40	1.12 (0.95 – 1.32)	Non-inferior
Blood feeding rate PC1 12 months	Non-inferiority	1.59	1.24 (1.19 – 1.29)	Non-inferior	Non-inferiority	1.67	0.94 (0.90 – 0.98)	Non-inferior	Non-inferiority	1.63	1.08 (1.05 – 1.11)	Non-inferior
Blood feeding rate PC2 3 months	Non-inferiority	1.38	1.39 (1.11 – 1.74)	Not non-inferior	Non-inferiority	1.36	2.08 (1.61 – 2.68)	Not non-inferior	Non-inferiority	1.37	1.54 (1.31 – 1.81)	Not non-inferior
Blood feeding rate PC2 12 months	Non-inferiority	1.89	0.86 (0.82 – 0.89)	Non-inferior	Non-inferiority	1.65	0.88 (0.85 – 0.92)	Non-inferior	Non-inferiority	1.74	0.87 (0.85 – 0.95)	Non-inferior
Benin												
M168 PC1 12 months	Non-inferiority	0.7	2.49 (2.10 – 2.95)	Superior	Non-inferiority	0.7	3.38 (2.90 – 3.94)	Superior	Non-inferiority	0.7	1.80 (1.53 – 2.11)	Superior
Ghana												
M72 PC2 13 months	Non-inferiority	0.735	0.53 (0.28 – 1.03)	Not non-inferior	Non-inferiority	0.724	2.30 (1.09 – 4.87)	Non-inferior	-	-	-	-

Table 3. 72- or 168-hour mortality (%) for WHO cone tests conducted in experimental huts treated with 120mg AI/m² of SOVRENTA 15WP, 300mg AI/m² of PC1 or 1,000 mg AI/m² of PC2 against insecticide susceptible and pyrethroid resistant test systems in Tanzania, Benin and Ghana.

Treatment	Substrate	Dose (mg AI/m²)	Month													
			0.25	1	2	3	4	5	6	7	8	9	10	11	12	13
Tanzania (*An. gambiae* Ifakara, M168)																
Control	Concrete	N/A	0	4 (0 – 12)	2 (0 – 6)	8 (0 – 18)	0	2 (0 – 6)	0	2 (0 – 6)	0	2 (0 – 6)	0	4 (0 – 9)	0	-
	Mud	N/A	2 (0 – 6)	0	2 (0 – 6)	6 (0 – 14)	2 (0 – 6)	4 (0 - 9)	2 (0 – 6)	2 (0 – 6)	4 (0 – 9)	0	0	4 (0 – 9)	0	-
SOVRENTA 15WP	Concrete	120	100	100	100	100	100	100	100	100	100	100	100	100	100	-
	Mud	120	100	100	100	100	100	100	100	100	100	100	100	100	100	-
PC1	Concrete	1,000	98 (94 – 100)	100	90 (75 – 100)	100	100	68 (54 – 82)	92 (85 – 99)	90 (79 – 100)	88 (81 – 95)	70 (44 – 96)	38 (27 – 49)	74 (64 – 84)	68 (44 – 92)	-
	Mud	1,000	100	98 (94 – 100)	100	100	100	76 (49 – 100)	100	88 (74 – 100)	100	90 (84 – 96)	96 (91 – 100)	72 (61 – 83)	90 (84 – 96)	-
PC2	Concrete	300	100	100	100	100	100	100	100	100	64 (54 – 74)	98 (94 – 100)	86 (76 – 96)	100	100	-
	Mud	300	100	100	100	100	100	98 (94 – 100)	92 (81 – 100)	94 (89 – 99)	96 (91 – 100)	86 (71 – 100)	58 (47 – 69)	100	100	-
Tanzania (*An. arabiensis* Kingani, M168)																
Control	Concrete	N/A	0	6 (0 – 14)	4 (0 – 9)	0	0	2 (0– 6)	0	0	0	0	0	0	0	-
	Mud	N/A	4 (0 – 12)	2 (0– 6)	2 (0– 6)	0	0	2 (0– 6)	0	0	0	0	0	2 (0– 6)	0	-
SOVRENTA 15WP	Concrete	120	100	100	100	100	100	100	100	100	100	100	100	98 (94 – 100)	100	-
	Mud	120	100	100	100	100	100	100	100	100	100	98 (94 – 100)	100	96 (91 – 100)	100	-
PC1	Concrete	1,000	100	100	86 (71 – 100)	72 (55 – 89)	86 (74 – 98)	56 (43 – 69)	68 (57- 79)	90 (81 – 98)	90 (81 – 99)	46 (38 – 54)	28 (17 – 39)	72 (65 – 79)	30 (24 – 36)	-
	Mud	1,000	100	100	80 (68 – 92)	68 (52 – 84)	80 (66 – 94)	62 (51 – 73)	60 (42 – 78)	86 (76 – 96)	10 (4 – 16)	40 (25 – 55)	36 (19 – 53)	74 64 – 84)	38 (34 – 42)	-

Table 3. 72- or 168-hour mortality (%) for WHO cone tests conducted in experimental huts treated with 120mg AI/m² of SOVRENTA 15WP, 300mg AI/m² of PC1 or 1,000 mg AI/m² of PC2 against insecticide susceptible and pyrethroid resistant test systems in Tanzania, Benin and Ghana.

Treatment	Substrate	Dose (mg AI/m²)	Month													
			0.25	1	2	3	4	5	6	7	8	9	10	11	12	13
PC2	Concrete	300	100	100	100	100	100	100	100	100	100	100	96 (91 – 100)	98 (94 – 100)	96 (91 – 100)	-
	Mud	300	100	100	100	100	96 (88 – 100)	98 (94 – 100)	88 (81 – 95)	92 (85 – 99)	90 (84 – 96)	66 (38 – 94)	20 (11 – 29)	94 (86 – 100)	92 (85 – 99)	-
Benin (*An. gambiae* Kisumu, M168)																
Control	Cement	N/A	2 (0 – 6)	2 (0 – 6)	2 (0 – 6)	2 (0 – 6)	0	0	0	0	6 (0 – 13)	4 (0 – 9)	4 (0 – 9)	4 (0 – 9)	4 (0 – 9)	-
SOVRENTA 15WP	Cement	120	100	100	100	100	100	100	100	100	100	100	100	100	100	-
	Mud	120	100	100	100	100	100	100	100	100	100	100	100	100	100	-
PC1	Cement	1,000	100	100	100	100	100	96 (91 – 100)	100	100	100	100	73 (61 - 85)	70 (58 – 82)	64 (51 – 77)	-
	Mud	1,000	100	100	100	100	100	100	100	100	100	100	54 (41 – 67)	52 (39 – 65)	50 (37 – 63)	-
Benin (*An. gambiae* Covè, M168)																
Control	Cement	N/A	0	0	0	0	0	2 (0 – 6)	0	4 (0 – 9)	6 (0 – 13)	2 (0 – 6)	2 (0 – 6)	2 (0 – 6)	2 (0 – 6)	-
SOVRENTA 15WP	Cement	120	100	100	100	100	100	100	100	100	100	100	100	98.3 (94.9-100)	97.2 (94.4-99.9)	-
	Mud	120	100	100	100	100	100	100	100	100	100	100	100	99 (97-100)	97.2 (93.1-100)	-
PC1	Cement	1,000	100	100	100	100	100	100	100	100	100	98 (94 – 100)	62 (49 – 75)	60 (47 – 73)	46 (33 – 59)	-
	Mud	1,000	100	100	100	100	100	100	100	100	100	100	56 (43 – 70)	50 (37 – 63)	44 (31 – 58)	-
Ghana (*An. gambiae* Kisumu, M72)																
SOVRENTA 15WP	Cement	120	100	98.1 (93.4 - 100)	100	100	100	100	100	100	100	100	100	100	100	68.3 (56.1 - 80.6)

Table 3. 72- or 168-hour mortality (%) for WHO cone tests conducted in experimental huts treated with 120mg AI/m² of SOVRENTA 15WP, 300mg AI/m² of PC1 or 1,000 mg AI/m² of PC2 against insecticide susceptible and pyrethroid resistant test systems in Tanzania, Benin and Ghana.

Treatment	Substrate	Dose (mg AI/m²)	Month													
			0.25	1	2	3	4	5	6	7	8	9	10	11	12	13
	Mud	120	98.3 (94.1 - 100)	86.7 (82.5 - 97.6)	100	96.7 (91.3 - 100)	100	100	100	100	100	100	100	98.3 (94.1 - 100)	100	85.0 (75.5 - 100)
	Tarpaulin	120	100	95.0 (90 - 100)	100	100	100	100	100	100	100	100	100	100	100	85.0 (76.4 - 100)
PC2	Cement	300	100	96.7 (82.3 - 100)	100	100	100	100	100	100	100	100	100	100	100	93.3 (64.6 - 100)
	Mud	300	93.3 (86.7 - 100)	96.7 (93.4 - 100)	100	100	100	100	100	100	100	100	73.3 (46.7 - 100)	100	100	100
	Tarpaulin	300	95.0 (90 - 100)	94.4 (88.9 - 100)	100	100	100	100	100	100	100	100	100	90.0 (80 - 100)	100	100
Ghana (*An. gambiae* Kulaa, M72)																
SOVRENTA 15WP	Cement	120	100	98.3 (94 - 100)	100	-	-	-	100	100	94.0 (82.9 - 100)	96.0 (89.2 - 100)	90.0 (72.4 - 100)	93.0 (81.5 - 100)	-	41.7 (29.4 - 53.9)
	Mud	120	98.3 (94.1 - 100)	98.3 (94.1 - 100)	100	-	-	-	100	100	100	86.7 (78.3 - 100)	100	96.7 (93.4-100)	-	50.0 (35.2 - 64.9)
	Tarpaulin	120	100	100	100	-	-	-	100	95.0 (31.5 - 100)	97.5 (89.6 - 100)	85.0 (54.6 - 94.6)	90.0 (71.7 - 95.8)	90.0 (67.5 - 97.1)	-	52.5 (32.5 - 72.6)
PC2	Cement	300	100	100	100	-	-	-	100	100	75.0 (50.9 - 91.3)	93.3 (64.6 - 100)	100	66.7 (38 - 95.4)	-	33.3 (19 - 47.7)
	Mud	300	100	100	100	-	-	-	100	100	85.0 (80 - 100)	46.7 (40 - 75.4)	100	90.0 (84.3 - 100)	-	80.0 (74.3 - 100)
	Tarpaulin	300	100	100	100	-	-	-	100	100	60.0 (54.6 - 70)	60.0 (40 - 100)	100	90.0 (67.1 - 100)	-	70.0 (57.1 - 80)
Ghana (*An. gambiae* Tiassale, M72)																
SOVRENTA 15WP	Cement	120	-	96.7 (91.2 - 100)	-	98.3 (94 - 100)	-	-	100	-	-	-	100	-	100	-

Table 3. 72- or 168-hour mortality (%) for WHO cone tests conducted in experimental huts treated with 120mg AI/m² of SOVRENTA 15WP, 300mg AI/m² of PC1 or 1,000 mg AI/m² of PC2 against insecticide susceptible and pyrethroid resistant test systems in Tanzania, Benin and Ghana.

Treatment	Substrate	Dose (mg AI/m²)	Month													
			0.25	1	2	3	4	5	6	7	8	9	10	11	12	13
	Mud	120	-	98.3 (96.7 - 100)	-	100	-	-	100	-	-	-	100	-	100	-
	Tarpaulin	120	-	97.5 (89.6 - 100)	-	100	-	-	100	-	-	-	100	-	100	-
PC2	Cement	300	-	100	-	100	-	-	100	-	-	-	100	-	100	-
	Mud	300	-	100	-	100	-	-	100	-	-	-	100	-	73.3 (46.7 - 100)	-
	Tarpaulin	300	-	100	-	100	-	-	100	-	-	-	100	-	50.0 (35 - 65)	-

2.2 Semi-field studies conclusions

The submitted semi-field studies demonstrate the bioavailability of isocycloseram on concrete/cement, mud and tarpaulin substrates using WHO cone bioassays and the impact of SOVRENTA 15WP on the mortality of free-flying mosquitoes in three locations. Based on the semi-field results in the submitted studies, following a single application of SOVRENTA 15WP at 120 mg AI/m^2, the bioavailability of isocycloseram can be sustained for up to 12 months on concrete/cement, mud and tarpaulin substrates against free-flying pyrethroid resistant *An. gambiae* s.l. and colonised insecticide susceptible and pyrethroid resistant *An. gambiae spp.*

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 biological impact and residual efficacy of the product on wall substrates.

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

Table 4. List of studies related to efficacy submitted to WHO as part of the prequalification dossier.

Studies that were relied upon for decision making	
Study number	**Study title**
BIT094 P2_PPMG22100	Experimental hut study of SYN547407 against resistant *Anopheles arabiensis* in Tanzania
22-03-B/GLP PPMG22102	Experimental hut evaluation of SYN547407 WP (A23752B) (by Syngenta Crop Protection AG) for indoor residual spraying against-pyrethroid resistant *Anopheles gambiae* s.l. in Covè, Southern Benin
PPME22853	Evaluation of the efficacy of SYN547407 15WP (A23752B) an Isocycloseram formulation for IRS against wild populations of *Anopheles gambiae* in Ghana
Studies that were not used to inform decision making	
Study number	**Study title**
	None