Randomized clinical trial to assess the protective efficacy of a *Plasmodium vivax* CS synthetic vaccine

Supplemental Material

Appendix 2

Paraclinical Safety Tests

Safety paraclinical tests were taken at the time of recruitment (selection), at the first immunization (month 0), after the first immunization (month 1), before the second (month 2), after the second immunization (month 3), before the third (month 6) and after the third (pre-challenge).

Paraclinical safety alterations during immunizations totaled 191 and consisted of: Anemia 24% (46), hematuria 15% (29), hyperglycemia 12% (23), proteinuria 9% (17), prolonged partial thromboplastin time 8 % (16), eosinophilia 7% (14), elevation of glutamic pyruvic transaminase 7.3% (14), prolongation of thrombin times 6% (11), elevation of indirect bilirubin without alteration of the AST/ALT pattern 2% (4), glutamic oxaloacetic transaminase elevation 1% (2), Leukocytopenia 3% (6), Leukocytosis 2% (4), Neutropenia 2% (4).

Indirect bilirubin up to 0.83mg / dL				
	CS1018	**CS1025**	**CS1030**	**CS1535**
Selection	0.08	0.13	0.28	0.28
Lab Control Month 0	0.34	0.10	0.88	0.04
Lab Control Month 1	0.02	0.06	0.2	0.22
Lab Control Month 2	0.1	0.86	0.12	0.13
Lab Control Month 3	0.16	0.05	0.58	0.1
Lab Control Month 6	0.9	0.10	0.11	0.88
Lab Control Pre- challenge	0.11	0.08	0.02	0.01

Table 4. Indirect bilirubin in the paraclinical follow-up of immunized volunteers who presented an adverse event (AE)

Renal function:

There was no alteration in renal function: creatinine and urea nitrogen values. All values were within the Protocol's standard ranges.

Glycemia:

There was a glycemia elevation in 17 volunteers in the selection paraclinical and on the first day of immunization. However, despite the request to present fasting for volunteers, some paraclinical were not taken on an empty stomach. Volunteers took their glycemia levels when they had time disposition. To determine glycemia, it was pertinent to measure fasting glucose levels or with a glucose tolerance curve.

	Selection	Grade	Lab Control Month 0	Grade
CS1001	121	1		
CS1003	104		126	2
CS1015	123	1	99	
CS1018	113	1	110	1
CS1036	110	1		
CS1037	110	1		
CS1506	111	1	117	1
CS1535	87		156	2
CS1537	77		124	1
CS1538	94		152	2
CS1547	95		119	1
CS1549	97		130	2
CS1553	87		112	1
CS1554	90		121	1
CS1565	111	1	119	1

CS1570	101		125	1
CS1572	92		113	1
CS1575	97		112	1
CS1581	110	1	110	1

Table 5. Glycemia in the paraclinical follow-up of immunized volunteers who presented an AE.

Transaminases:

Grade 1 transaminase elevation (ALT and AST) (elevation 1.1-2.5 ULN) occurred in 7 volunteers (CS1575, CS1025, CS1030, CS1031, CS1538, CS1570, CS1581).

Elevated Glutamic Pyruvic Transaminase:

Grade 1 elevation (elevation 1.1-2.5 ULN) occurred in 7 volunteers. Bearing in mind that the reference values vary according to whether you are male or female. In men's case, the reference value is Up to 40 U / L; therefore, a Grade 1 AE corresponds to an elevation greater than 44 U / L in the case of men (CS 1575). In the case of women, the reference value is up to 32 U / L. Therefore, AE Grade 1 corresponds to values higher than 35 (CS1025, CS1031, CS1538, CS1570, CS1581). Altered values at the time of selection are not related to immunizations due to temporality; subsequent elevations may or may not be related.

It should be noted that the volunteer CS1565 and CS1538 presented elevations in glutamic pyruvic transaminase from the beginning of the study before the administration of the immunization. Both belong to the experimental group. Volunteers CS1025, CS1030, CS1031, CS1575, CS1581 were part of the experimental group. Volunteer CS1570 belonged to the control group.

Glutamic Pyruvic Transaminase U / L								
Moment	**CS1025**	**CS1031**	**CS1538**	**CS1565**	**CS1570**	**CS1575**	**CS1581**	**Grado**
Selection	31	31	39	39	26	29	28	1
Lab Control Month 0	33	24	50	25	13	40	28	1

Lab Control Month 1	54	22	61	22	20	41	23	1
Lab Control Month 2	22	48	53	19	15	41	36	1
Lab Control Month 3	25	31	59	29	12	27	27	1
Lab Control Month 6	38	52	19	23	28	80	19	1
Lab Control pre-challenge	26	14	72	31	53	37	15	1

Table 6. Glutamic Pyruvic transaminase in the paraclinical follow-up of immunized volunteers who presented an AE.

Elevation of glutamic oxaloacetic transaminase:

There was no evidence of elevated SGOT in any male volunteers from the moment of recruitment until the safety paraclinical after the third immunization.

Volunteer CS1538, who belonged to the experimental group, presented Grade 1 elevation of the SGOT in control paraclinical after the first and third immunization.

Glutamic Oxaloacetic Transaminase (SGOT) Woman Reference value: 8-39 U/L		
	CS1538	**Grade**
Selection	34	1
Lab Control Month 0	40	1
Lab Control Month 1	51	1
Lab Control Month 2	40	1
Lab Control Month 3	43	1

Lab Control Month 6	23	1
Labo Control pre-challenge	46	1

Table 7. Glutamic Oxalacetic Transaminase in the paraclinical follow-up of immunized volunteers who presented an AE.

Clotting times:

Prothrombin time: (standard value 12-15 sec)

There was a slight prolongation considering a Grade I adverse event in 9 volunteers, of which eight corresponded to the experimental group (CS1006, CS1015, CS1028, CS1031, CS1036, CS1506, CS1565, CS1575) and 1 to the control group (CS1037).

However, two volunteers who belong to the experimental group and one who belongs to the control group presented prolonged selection paraclinical.

PT VN 12-15 sec	**CS1006**	**CS1015**	**CS1028**	**CS1031**	**CS1036**	**CS1037**	**CS1506**	**CS1565**	**CS1575**
Selection	8.3	9.5	13.7	8.4	13.6	14.2	9.7	8.3	9.6
Lab Control Month 0	8.2	9.3	9.1	8.4	8.2	8.70	9.5	8.6	8.3
Lab Control Month 1	9.8	9.2	8.7	10.2	8.5	10.3	8.2	9.2	9.3
Lab Control Month 2	8.6	10.8	10.4	9.8	10.5	8.3	11.2	9.4	10.0
Lab Control Month 3	11.0	9.8	9.9	11.1	9.8	9.5	9.5	11.0	11.0

Lab Control Month 6	8.7	9.9	9.2	8.5	8.5	9.8	9.0	11.1	8.9
Lab Control pre-challenge	9.8	9.0	9.3	8.2	9.8	9.6	11.8	10.2	7.5
Grade	1	1	4	1	4	4	1	1	1

Table 8. Prothrombin time in the paraclinical follow-up of immunized volunteers who presented an AE.

Partial Thromboplastin Time (PTT):

(normal value 25-35 sec)

There was an alteration in the partial thromboplastin time values, following the Protocol's adverse event values in 14 volunteers.

10 volunteers (CS1023, CS1028, CS1031, CS1038, CS1506, CS1511, CS1537, CS1547, CS1553, CS1565) belonged to the experimental group 4 volunteers (CS1037, CS1549, CS1554, CS1574).

However, 4 volunteers of the 14 who presented prolongation of the TTP showed this alteration in the selection paraclinical. Of these three volunteers correspond to the experimental group and one to the control group.

PTT VN 25-35 sec	**CS1023**	**CS1028**	**CS1031**	**CS1037**	**CS1038**	**CS1506**	**CS1511**	**CS1537**	**CS1547**	**CS1549**
Selection	31.1	36.5	31.8	36.7	22.3	24.8	22.9	30.2	26.8	28.3
Lab Control Month 0	24.8	25.3	28.6	22.70	22.80	28.8	22.3	28.2	27.4	24.8

Lab Control Month 1	26.9	23.3	28.6	26.7	26.1	24.3	26.7	23.6	23.6	22.2
Lab Control Month 2	25.3	29.9	26.2	26.6	27.1	27.2	26.5	25.3	27.7	28.1
Lab Control Month 3	23.1	25.4	27.1	26.2	27.1	25.1	26.1	26.1	26.1	22.1
Lab Control Month 6	25.3	27.9	30.1	25.5	32.0	31.0	27.9	26.5	30.7	35.7
Lab Control pre-challenge	22.8	24.6	22.3	24.9	28.5	31.9	31.8	34.5	37.7	39.3
Grade	1	1	1	1	1	1	1	1	1	1
Grade						1			2	2

Table 9. Partial thromboplastin time in the paraclinical follow-up of immunized volunteers who presented an AE.

Hemogram:

Anemia:

The Protocol's reference values to categorize anemia are Hb less than or equal to 12g / dL in women and less than or equal to 13.5g / dL in men.

Thirteen volunteers presented a slightly low hemoglobin value ranging from 11.2 - 11.8 g / dL in 10 women and three men. Among 9 volunteers (CS1005, CS1012, CS1013, CS1028, CS1511, CS1537, CS1549, CS1574, CS1581), 10 presented Grade 1 classification and only 2 volunteers were found in Grade 2. Among the men, only one volunteer presented Grade I anemia (CS1572).

Anemia													
	CS1005	**CS1006**	**CS1012**	**CS1013**	**CS1028**	**CS1511**	**CS1537**	**CS1547**	**CS1549**	**CS1572**	**CS1575**	**CS1574**	**CS1581**
Selection	12.5	12.50	12.00	10.80	12.30	11.50	12.70	14.70	12.30	12.90	13.70	12.80	12.10
Lab Control Month 0	12.70	12.60	11.20	11.80		11.80	12.20	14.50	12.10	13.20	14.00	12.20	12.10
Lab Control Month 1	13.20	12.40	11.70	11.60	12.40	11.40	11.60	13.50	11.30	12.80	14.10	12.20	10.40
Lab Control Month 2	12.80	12.50	11.10	11.50	11.60	11.20	12.10	14.20	10.60	13.30	13.70	12.00	11.20
Lab Control Month 3	11.30	12.00	11.20	12.60	13.00	11.10	12.30	14.90	11.50	12.10	16.10	12.20	11.30
Lab Control Month 6	12.50	12.40	11.50	11.90	11.60	11.60	12.00	14.20	10.70	12.80	13.30	11.90	11.50
Lab Control pre-challenge	13.00	13.20	11.80	13.10	12.60	11.30	11.90	14.50	12.10	13.10	14.00	12.00	12.30

Grade	1	1	1	2	1	1	1	1	2	1	1	1	2

Table 10. Hemoglobin in the paraclinical follow-up of immunized volunteers who presented an AE.

Thrombocytopenia:
Thrombocytopenia was not evidenced in the volunteers during the immunizations, considering the reference values of the Protocol.

Leukocytopenia:
He had Grade 1 leukopenia (3500-2500 cells / mm3), 3 volunteers (CS1006, CS1013 and CS1025). Volunteer CS1006 and CS1013 belonged to the experimental group.

Leukocytopenia (Reference value: <3500)				
	CS1006	**CS1013**	**CS1025**	
Selection	7.40	4.30	5.10	**Grade**
Lab Control Month 0	3.40	7.10	4.80	1
Lab Control Month 1	3.60	3.30	5.30	1
Lab Control Month 2	3.20	6.40	6.20	1

Lab Control Month 3	4.00	4.40	3.50	1
Lab Control Month 6	3.10	10.60	7.00	1
Lab Control pre-challenge	2.80	4.30	5.30	1

Table 11. Leukopenia in the paraclinical follow-up of immunized volunteers who presented an AE

Leukocytosis:

Three volunteers presented Grade I leukocytosis at four times, following the reference values of the Protocol. Volunteers CS1015, CS1535 and CS1537 belonged to the experimental group.

Leukocytosis (Reference values >10.800)				
	CS1015	**CS1535**	**CS1537**	**Grade**
Selection	5.5	12.10	9.4	1
Lab Control Month 0	7.20	11.40	11.80	1
Lab Control Month 1	10.90	8.90	6.70	1
Lab Control Month 2	5.60	8.00	5.80	
Lab Control Month 3	4.60	8.60	6.50	

Lab Control Month 6	7.00	10.30	8.20	
Lab Control pre-challenge	4.70	7.90	8.70	

Table 12. Leukocytosis in the paraclinical follow-up of immunized volunteers who presented an AE

Lymphopenia:

Lymphocyte levels below the ranges determined by the Protocol that characterize lymphopenia were not evidenced in volunteers during immunizations.

Neutropenia:

Three volunteers from the experimental group had mild neutropenia (CS1013, CS1006, CS1025),

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Time	CS1006	CS1013	CS1025
Selection	6.00	2.40	2.50
Lab Control Month 0	1.80	4.50	2.00
Lab Control Month 1	1.90	1.20	
Lab Control Month 2	1.10	3.90	
Lab Control Month 3	1.90	2.60	1.30
Lab Control Month 6	1.60	7.50	

Lab Control pre-challenge	1.10	2.70	3.60
Grade	1	1	1

Table 13. Neutropenia in the paraclinical follow-up of immunized volunteers who presented an AE

Eosinophilia:

Within the reported values, five volunteers had Grade I eosinophilia, and one volunteer had Grade II eosinophilia at four times. Four volunteers belonged to the control group (CS1018, CS1554, CS1572, CS1574) and 5 to the experimental group (CS1023, CS1511, CS1535, CS1538, CS1569).

	CS1018	**CS1023**	**CS1511**	**CS1535**	**CS1538**	**CS1554**	**CS1569**	**CS1572**	**CS1574**
Selection	**0**	728,0	**0**	1089,0	888,0	344,0	288,0	882,0	768,0
Lab Control Month 0	1332,0	0	84,0	228,0	288,0	87,00	110,0	448,0	2765,0
Lab Control Month 1	602,0	0	0,0	1157,0	0	0	116,0	171,0	2160,0
Lab Control Month 2	0	0	249,0	560,0	0	552,0	0	58,0	2263,0

Lab Control Month 3	62,0	210,0	0,0	258,0	0	345,0	348,0	0	1932,0
Lab Control Month 6	0	0	675,0	0	0	711,0	1050,0	462,0	0
Lab Control pre-challenge	0	0	0	0	0	0	0	0	0
Grade	1	1	1	1	1	1	1	1	

Table 14. Eosinophilia in the paraclinical follow-up of immunized volunteers who presented an AE.

Urinalysis:

Proteinuria:

Proteinuria was found in 13 volunteers. Of these, 3 had proteinuria in paraclinical on the day of immunization.

Proteinuria was classified as Grade 1 (trace) in 4 volunteers (CS1006, CS1036, CS1037, CS1047); Grade 2 (+) in 5 volunteers (CS1001, CS1005, CS1012, CS1030, CS1038) and Grade 1 and 2 in 4 volunteers (CS1003, CS1015, CS1018, CS1031).

Of these, 8 volunteers belonged to the experimental group (CS1001, CS1006, CS1015, CS1030, CS1031, CS1036, CS1038, CS1547) and 5 to the control group (CS1003, CS1005, CS1012, CS1018, CS1037)

	CS1001	**CS1003**	**CS1005**	**CS1006**	**CS1012**	**CS1015**	**CS1018**	**CS1030**	**CS1031**	**CS1036**	**CS1037**	**CS1038**	**CS1547**

Selection	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Lab Control Month 0	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Pos		Neg	Neg	Neg	Neg
Lab Control Month 1	Pos	Neg	Pos	Pos	Pos	Pos	Neg	Neg	Pos	Neg	Neg	Neg	Neg
Lab Control Month 2	Neg	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Neg	Pos
Lab Control Month 3	Neg	Neg		Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Neg	Neg
Lab Control Month 6	Neg	Pos		Neg	Neg	Neg	Neg	Neg	Pos	Neg	Neg	Pos	Neg

Table 15. Proteinuria in the paraclinical follow-up of immunized volunteers who presented an AE

Glycosuria:

He presented severe glycosuria (500mg / dL) in volunteer CS1584, subsequently diagnosed with diabetes mellitus (HbA1c: 8.1%).

Hematuria:

Hematuria was mild in 14 volunteers at 26 moments classified as Grade I. In two moments, it was classified as Grade II (Lab control month 0 in CS1569 and Lab control pre-challenge in CS1038).

	Selection	**Lab Control Month 0**	**Lab Control Month 1**	**Lab Control Month 2**	**Lab Control Month 3**	**Lab Control Month 6**	**Lab Control**	

							pre-challenge	
Code	**Erythrocytes**	**Erythrocytes**	**Erythrocytes**	**Erythrocytes**	**Erythrocytes**	**Erythrocytes**	**Erythrocytes**	**Classification EA**
CS1005	0	-	-	5 - 8 xc	NA	NA	-	Grade I
CS1012	0-2xc	3-5xc	-	-	-	-	-	Grade I
CS1013	4-6xc	NA	5 xc	5 xc	1 xc	1 xc	eumorphs	Grade I
CS1023	*-	0-1xc	-	-	-	-	-	Grade I
CS1031	-		0-2 xc	-	-	-	-	Grade I
CS1037	0-2xc	0	3	5-8 xc	-	-	-	Grade I
CS1038	-	-	-	-	-	-	8-12xc	Grade I
CS1506	0-1xc	-	-	-	-	-	0 eumorphs	Grade I
CS1535	0-2xc	-	-	-	-	2 xc	2 xc	Grade I

CS1537	-	0-2 xc	5 xc	-	-	-	-	Grade I
CS1549	0	0	0	0	-	0	2 xc	Grade I
CS1565	0-2 xc	-	-	-	-	-	2xc	Grade I
CS1569	1-3xc	>25 xc eu, 1-3xc dis	-	-	-	5xc	0	Grade I-II
CS1575	2-4 xc	2 xc	5 xc	-	-	-	-	Grade I

Table 16. Hematuria in the paraclinical follow-up of immunized volunteers who presented an AE

Clinical manifestations after the Infectious Challenge (CHMI)

As expected, there were symptoms and signs of malaria infection.

Arthralgia: Of the 32 volunteers exposed to the infectious challenge, on eight occasions, they reported arthralgia in the face-to-face and telephone medical follow-ups after the infectious challenge. 75% of the time was related to the infectious challenge, and 12.5% of the time possibly and probably related.

Deterioration: On 16 occasions, the volunteers exposed to the infectious challenge reported deterioration, which was related in 43% (7/16) of the cases, possibly in 13%, and probably in 43% (7/16) infectious challenge.

Diaphoresis: On one occasion, a volunteer presented diaphoresis with hypotension (TA: 80/50), which responded to intravenous fluids.

Diarrhea: On five occasions, some volunteers had diarrhea which was found to be possibly related in 40% (2/5), in 40% (1/5) probably related, and 20% (1/5) probably unrelated to the infectious challenge.

Abdominal pain: On seven occasions, they had abdominal pain. Of these 28% (2/7) presented in the epigastrium and 72% (5/7) it was not specified, also in 28% (2/7) of the cases were considered probably related, in 14% (1/7) possibly related, in 28% (2/7), probably not related, in 14% (1/7) not related to the infectious challenge; in one case it was not specified.

Headache: Headache was reported on 48 occasions after the infectious challenge, of these: in 16% (8/48), it was considered related, in 29% (14/48), it was considered probably related, in the 20% (10/48) was considered possibly related, in 18% (9/48) it was considered probably unrelated, in 8% (4/48) it was deemed to be unrelated, there is no data for 6% (3 / 48).

Arm pain: In 85% (6/7), it was considered not related to the infectious challenge, and in 15% (1/7), it was considered related to the infectious challenge.

Chills: On 21 occasions, the volunteers had chills. In 76% (16/21), it was considered related, in 4% (1/21) probably related, in 4% (1/21) possibly related, and in the 14% (3/21) probably unrelated.

Fever: On 20 occasions, the volunteers presented fever after the infectious challenge. It was considered in 85% (17/20) related and in 15% probably unrelated (3/20).

Insomnia: On one occasion, insomnia occurred, which was considered possibly related to the infectious challenge.

General discomfort: On 41 occasions, the volunteers presented general discomfort. It was considered: in 39% (16/41) related, in 7% (3/41) probably related, in 7% (3/41) possibly related, in 20% (8/41) probably not related, in 2% (1/41) not related to the infectious challenge. However, in ten cases (24%), the general malaise was not related to the infectious challenge.

Myalgias: On 23 occasions, the volunteers presented myalgias. It was considered: in 61% (14/23) related, in 9% (2/23) probably related, in 17% (4/23) possibly related, probably 13% (3/23) unrelated to the CHMI.

Nausea: On 20 occasions the volunteers had nausea, it was considered: in 5% (1/20) related, in 50% (10/20) probably related, in 20% (4/20) possibly related, in 15% (3/20) probably unrelated, in 10% (2/20) unrelated.

Itching: On two occasions, itching was reported, which was not related to the infectious challenge or treatment.

Urticaria: On two occasions, the volunteers presented urticaria (20 minutes), which was not related to the CHMI but rather to the xenodiagnosis. Urticaria lasting 4 min, unrelated to the CHMI, was also reported on one occasion.

Blurred vision: Blurred vision was reported on six occasions. It was considered: in 83% (5/6) possibly related, and in 17% (1/6) probably not related to the CHMI.

Others: 29 findings were reported as others which are recognized as alterations in the area of exposure to xenodiagnosis, the clinical picture of dyspnea and cough in treatment with salbutamol, viral vision, emesis, dizziness, myalgia of the lower limbs, dyspnea predominantly nocturnal, possible origin psychosomatic, cyst in the left ovary, rhinorrhea and earache, mild dizziness, dry cough, and vomiting.

Table 17. Clinical manifestations after the infectious challenge

Categorized Adverse Event	Description	Relationship to the Challenge	Relationship to Treatment	Total
Arthralgia	**NA**	Definitely related	Not related	5
			Probably unrelated	1

		Possibly related	Not related	1
		Probably related	Not related	1
	Total NA			**8**
Total Arthralgia				**8**
Decay	**NA**	Definitely related	Not related	7
		Possibly related	Not related	2
		Probably related	Not related	7
	Total NA			**16**
Total Decay				**16**
Diaphoresis	**Hypotension 80/50 responded to treatment with intravenous fluids**	NA	NA	1
	Total, hypotension 80/50 responded to treatment with intravenous fluids			**1**
	NA	Definitely related	Probably unrelated	1
	Total NA			**1**
Total Diaphoresis				**2**
Diarrhea	**NA**	Possibly related	Not related	1
			Possibly related	1
		Probably unrelated	Not related	1
		Probably related	Not related	1
			Possibly related	1
	Total NA			**5**
Total Diarrhea				**5**

Abdominal pain	**Abdominal pain in the epigastrium**	Probably unrelated	Not related	1
	Total, Abdominal pain in the epigastrium			**1**
	epigastric pain	Probably unrelated	Probably related	1
	Total, epigastric pain			**1**
	NA	NA	NA	1
		Not related	Possibly related	1
		Possibly related	Not related	1
		Probably related	Possibly related	1
			Probably related	1
	Total NA			**5**
Total Abdominal pain				**7**
Headache	**Global mild headache**	Probably unrelated	Probably related	1
	Total Global mild headache			**1**
	Migraine-like headache	Probably unrelated	Not related	1
	Total Migraine-like headache			**1**
	NA	Definitely related	Not related	6
			Possibly related	1
			Probably unrelated	1
		NA	NA	3
		Not related	Not related	2
			Possibly related	1
			Probably related	1

		Possibly related	Not related	9
		Probably unrelated	Not related	6
			Probably unrelated	1
		Probably related	Not related	14
	Total NA			**45**
	Refers mild headache	Possibly related	Not related	1
	Total Refers mild headache			**1**
Total Headache				**48**
Arm pain	**Pain in mosquito exposure area**	Not related	Not related	1
	Total pain in mosquito exposure area			**1**
	Pain in the area of exposure to xenodiagnosis	Not related	Not related	1
	Total pain in the area of exposure to xenodiagnosis			**1**
	Pain in the area of exposure to xenodiagnosis	Not related	Not related	1
	Total pain in the area of exposure to xenodiagnosis			**1**
	Pain in the area of exposure to xenodiagnosis	Not related	Not related	1
	Total pain in the area of exposure to xenodiagnosis			**1**
	Pain in the area of exposure to xenodiagnosis	Not related	Not related	1
	Total pain in the area of exposure to xenodiagnosis			**1**

	NA	Definitely related	Not related	1
	Total NA			**1**
	Patient who had an accident with a polisher with lesion in the left hand thenar region	Not related	Not related	1
	Total Patient who had an accident with a polisher with lesion in the left hand thenar region			**1**
Total arm pain				**7**
Chills	**NA**	Definitely related	Definitely related	1
			Not related	14
			Probably unrelated	1
		Possibly related	Not related	1
		Probably unrelated	Not related	3
		Probably related	Not related	1
	Total NA			**21**
Total Chills				**21**
Fever	**NA**	Definitely related	Not related	16
			Probably unrelated	1
		Probably unrelated	Not related	2
	Total NA			**19**
	Unquantified fever	Probably unrelated	Probably unrelated	1
	Total Unquantified fever			**1**
Total Fever				**20**
Insomnia	**NA**	Possibly related	Not related	1
	Total NA			**1**

Total Insomnia				**1**
Malaise	**Flu-like symptoms**	Not related	Not related	1
	Total flu-like symptoms			**1**
	Viral infection	Probably unrelated	Not related	1
	Total viral infection			**1**
	Malaise, flu-like symptoms	Possibly related	Not related	1
	Total malaise, flu-like symptoms			**1**
	NA	Definitely related	Not related	14
			Probably unrelated	2
		NA	NA	10
		Possibly related	Not related	1
		Probably unrelated	Not related	6
		Probably related	Not related	3
	Total NA			**36**
	Malaise	Probably unrelated	Probably unrelated	1
	Total again after three days general malaise begins			**1**
	General malaise spontaneous resolution	Possibly related	Not related	1
	Total refers to general discomfort yesterday, spontaneously resolved			**1**
Total Malaise				**41**
Myalgia	**NA**	Definitely related	Not related	13
			Probably unrelated	1
		Possibly related	Not related	4
		Probably unrelated	Not related	3

		Probably related	Not related	2
	Total NA			**23**
Total Myalgia				**23**
Other	**Alterations in the xenodiagnosis exposure area**	Not related	NA	1
	Total Alterations in the xenodiagnosis exposure area			**1**
	A clinical case of more than one month of evolution consisting of dyspnea associated with dry cough, apparently without triggers. Treated with salbutamol inhaler.	Probably unrelated	NA	1
	Total, A clinical case of more than one month of evolution consisting of dyspnea associated with dry cough, apparently without triggers. Treated with salbutamol inhaler.			**1**
	Flu-like symptoms	Not related	NA	1
	Total, Flu-like symptoms			**1**
	Pain at mosquito exposure site	Not related	NA	1
	Total, pain at mosquito exposure site			**1**
	Vomiting	Definitely related	NA	1
	Total, vomiting			**1**
	With fever	Probably unrelated	NA	1
	Total, with fever			**1**

Dizziness	Probably unrelated	NA	1
Total dizziness			**1**
Myalgia, only in lower limbs	Probably unrelated	NA	1
Total, myalgia, only in lower limbs			**1**
NA	Not related	NA	7
	Probably unrelated	NA	2
Total NA			**9**
Dyspnea, predominantly nocturnal in the sitting and ulnar position, is not exacerbated by exercise nor associated with respiratory symptoms. Possible psychosomatic origin is questioned, and it is decided to continue follow-up.	Not related	NA	1
Dyspnea, predominantly nocturnal in the sitting and ulnar position, is not exacerbated by exercise nor associated with respiratory symptoms. Possible psychosomatic origin is questioned, and it is decided to continue follow-up.			**1**
Flu-like symptoms	Probably unrelated	NA	1
Total Flu-like symptoms			**1**
Flu-like symptoms	Probably unrelated	NA	1

Total Flu-like symptoms			**1**
Probably of gynecological origin	Not related	NA	1
Total, Probably of gynecological origin			**1**
Cyst on the left side under follow-up by gynecology	Not related	NA	1
Cyst on the left side under follow-up by gynecology			**1**
Reports that dizziness is associated with the intake of primaquine.	Probably unrelated	NA	1
Total, Reports that dizziness is associated with the intake of primaquine.			**1**
Hyaline rhinorrhea / otalgia	Not related	NA	1
Total, Hyaline rhinorrhea /otalgia			**1**
Dizziness (feeling)	Possibly related	NA	1
	Probably unrelated	NA	1
Total, dizziness (feeling)			**2**
Mild dizziness (feeling)	Probably unrelated	NA	1
Total Mild dizziness (feeling)			**1**
Dry cough	Probably unrelated	NA	1
Total, dry cough			**1**
Vomiting	Probably related	NA	1
Total, vomiting			**1**

Total NA				**29**
Nausea	**NA**	Definitely related	Possibly related	1
		Not related	Not related	1
			Possibly related	1
		Possibly related	Not related	1
			Possibly related	1
			Probably unrelated	1
			Probably related	1
		Probably unrelated	Possibly related	1
			Probably related	1
		Probably related	Not related	7
			Probably related	3
	Total NA			**19**
	Nausea accompanying epigastric pain	Probably unrelated	Probably related	1
	Total, Nausea accompanying epigastric pain			**1**
Total Nausea				**20**
Pruritus	**1-week clinical picture of generalized itching, predominantly in the back.**	Not related	Not related	1
	Total, 1-week clinical picture of generalized itching, predominantly in the back.			**1**
	Pruritus in the xenodiagnosis area	Not related	Not related	1
	Total, Pruritus in the xenodiagnosis area			**1**

Total Pruritus				**2**
Urticaria (20 minutes)	**Pruritus in the xenodiagnosis area**	Not related	Not related	1
	Total, Pruritus in the xenodiagnosis area			**1**
	Maculopapular rash at the mosquito exposure site	NA	NA	1
	Total, Maculopapular rash at mosquito exposure site			**1**
Total Urticaria (20 minutes)				**2**
Urticaria (4 minutes)	**Pruritus in the exposure area**	NA	NA	1
	Total, Pruritus in the exposure area			**1**
Total Urticaria (4 minutes)				**1**
Blurred vision	**after taking antimalarials**	Probably unrelated	Possibly related	1
	Total, after taking antimalarials			**1**
	NA	Possibly related	Not related	3
			Possibly related	2
	Total NA			**5**
Total blurred vision				**6**
Total, general				**259**

Results of paraclinical in Infectious Challenge

The alterations in safety paraclinical during the CHMI were 27. They consisted of hyperglycemia 4% (1), the elevation of glutamic-pyruvic transaminase 19% (5), the elevation of indirect bilirubin without alteration of the AST / ALT pattern 4% (1), anemia 41 (11), leukopenia 11% (3), leukocytosis 11% (3), lymphopenia 4% (1), hematuria 7% (2). According to the FDA classification of AE, 85% of paraclinical AE during the infectious challenge correspond to Grade 1 and the remaining 15% to Grade 2. Safety paraclinical after the CHMI were taken on day 33 of the challenge.

Paraclinical results were registered in the RedCap database; the reference values were obtained from the Protocol. All recorded values were analyzed, and the paraclinical test alterations were classified according to the Protocol.

Glycemia: A fasting sample was taken. Therefore, the values were found in normal ranges. Volunteer CS1575 had blood glucose levels of 140 mg/dl, which would lead to a Grade I adverse event.

Creatinine and BUN: There was no elevation evidence to ranges considered an AE according to the protocol classification.

Transaminases: They presented Grade 1 elevation of Pyruvic Glutamic Transaminase, five volunteers of which 3 were women, and 2 were men. No elevation of Oxaloacetic Transaminases was evidenced in any of the volunteers after the challenge.

Volunteer	Value ALT (U/L)	Sex	Grade
CS1025	40	Woman	1
CS 1538	58	Woman	1
CS 1565	43	Woman	1
CS1015	54	Man	1
CS1575	74	Man	1

Table 18. Alteration in Glutamic Pyruvic and Oxaloacetic Transaminases

Direct bilirubin: No elevation was evidenced in post-challenge paraclinical.

Indirect bilirubin without alteration of the AST / ALT pattern: Only volunteer CS1506 presented Grade 1 elevation.

Paraclinical	Value
Bilirubin indirect	0.87
ALT	27
AST	29

Table 19. Indirect bilirubin alteration without compromise of the AST / ALT pattern

Prothrombin Time- Partial Thromboplastin Time: There were no alterations in clotting times

Blood count

On day 33, post-CHMI paraclinical tests indicated:

Anemia: 11 volunteers had mild anemia. According to the reference values of the protocol for the classification of the AE, seven volunteers (CS1005, CS1006, CS1554, CS1565, CS1570, CS1574, CS1581) had Grade 1 anemia (Hb 11-12 g / dL) and four volunteers (CS1511, CS1537, CS1549, CS1569) Grade 2 (Hb 9.5-10.9 g / dL):

Volunteer	Hemoglobin	Grade
CS1005	11.8	1
CS1006	11.7	1
CS1511	10.6	2
CS1537	10.3	2
CS1549	10.8	2
CS1554	11.4	1
CS1565	11.2	1
CS1569	10.4	2
CS1570	11.6	1
CS1574	11.8	1
CS1581	11.0	1

Table 20. Alteration in Hb values

Leukopenia: Grade 1 leukopenia was evidenced in three volunteers (CS1006, CS1028, CS1037).

Volunteer	Leucocytes /ul	Grade
CS1006	2800	1
CS1028	3000	1
CS1037	3000	1

Table 21. Leukopenia post-CHMI paraclinical follow-up.

Leukocytosis: Grade 1 leukocytosis was evidenced in three volunteers (CS1012, CS1547, CS1570).

Volunteer	Leucocytes /ul	Grade
CS1012	11.5	1
CS1570	11.2	1
CS1547	11.2	1

Table 22. Leukocytosis in post-CHMI paraclinical follow-up

Lymphopenia: In post-challenge paraclinical, only volunteer CS1006 had Grade 1 lymphopenia (896).

Thrombocytopenia: Thrombocytopenia was not evidenced.

Urine test

Glycosuria: in the RedCap report, there is no evidence of altered glucose values in urine.

Proteinuria: no proteinuria was evidenced in any of the volunteers post-CHMI.

Hematuria: Volunteer CS1013 and volunteer CS1553 presented Grade 1 hematuria.

	Selection	Lab Control Month 0	Lab Control Month 1	Lab Control Month 2	Lab Control Month 3	Lab Control Month 6	Lab Control pre-challenge	Challenge
Code	**Erythrocytes:**	**Erythrocytes:**	**Erythrocytes:**	**Erythrocytes:**	**Erythrocytes:**	**Erythrocytes:**	**Erythrocytes:**	**Erythrocytes:**
CS1013	4-6xc	-	5.00	5	1	1	eumorfos	5 eumorfos
CS1553	-	-	-	-	-	-	-	1 eumorfos

Table 23. Hematuria in post-challenge paraclinical follow-up

However, volunteer CS1013 from the selection paraclinical presented Grade I hematuria. There was likely no relationship between the hematuria post-CHMI and the investigation (immunizations and CHMI). Volunteer CS1553 presented Grade I hematuria on the lower levels.