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ORIGINAL ARTICLE

Age- and sex-related changes in body weights and clinical pathology analytes in cynomolgus monkeys (*Macaca Fascicularis*) of Mauritius origin

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Abstract

Background: Clinical pathology and body weight information for the cynomolgus monkey in the literature is primarily derived from a small number of animals with limited age ranges, varying geographic origins, and mixed genders.

Objectives: This study aimed to summarize the age- and sex-related changes in clinical pathology analytes and body weights in cynomolgus monkeys of Mauritian origin.

Methods: Pre-study age and body weight data were reviewed in 1819 animals, and pre-study hematologic, coagulation, and serum biochemical analytes were reviewed in 1664 animals.

Results: Body weights were statistically higher ($P < 0.01$) in males than females in all age groups (2–10 years). These measurements became prominent after 4 years of age and peaked at 7 to 8 years of age in both sexes. Sex-related differences were noted in reticulocyte (RETIC) counts, creatinine, cholesterol, and triglyceride concentrations, and alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) activities. Age-related differences were noted in RETIC and lymphocyte counts, creatinine, triglyceride, phosphorus, and globulin concentrations, and ALP and GGT activities. The youngest (2 to <3 year) age group had the fewest number of clinical pathologic analyte differences including ALP and GGT activity differences which occurred in all age groups from 2 to 10 years; they also had age-related lower globulin concentrations. There were no age- or sex-related differences in coagulation measurands.

Conclusions: Sexual dimorphism in body weight was apparent for all ages from 2 to 10 years of age. The only difference in clinical pathology analytes unique to the 2 to <3 years of age group were age-related lower globulin levels.

KEYWORDS
body weight, coagulation, cynomolgus monkey, hematology, Mauritius, serum biochemistry

1 | INTRODUCTION

Non-human primates (NHP) are the closest phylogenetic relatives of humans with similar physiologic traits; they especially resemble the anatomy and genetics of macaques and apes.[1,2] Of the 22 macaque species, 21 species are distributed in Asia, including cynomolgus and rhesus monkeys.[3,4] The cynomolgus monkey is recognized as having 10 subspecies based on their pelage colors and tail lengths. The cynomolgus monkey (*Macaca fascicularis*, *M. cynomolgus*, and *M. irus*) is also known as the long-tailed macaque or crab-eating macaque.

The cynomolgus monkey is distributed primarily in Southeast Asia.[2,3] Cynomolgus monkeys that inhabit the north of the Isthmus of Kra might have genetic introgression from the rhesus monkey in Cambodia, Laos, Myanmar, Thailand, and Vietnam, whereas those that inhabit the south of the Isthmus would have no genetic influences from the rhesus monkey.[5,6] The cynomolgus monkey in Mauritius was introduced from Indonesia by shipping trades around the 16th century.[7] The original founder population was estimated at approximately 10 to 15 monkeys.[8] Thus, the genetic diversity of Mauritius monkeys is low.[5] The cynomolgus monkey in China was introduced from Vietnam, Cambodia, Laos, and Myanmar in the late 1980s.[4] Mauritius cynomolgus monkeys were shown to have differences in some hematologic and biochemical analytes and lower grades and incidences of background pathologic changes than Asian cynomolgus monkeys.[9,10] Cynomolgus monkeys of Mauritian origin become sexually mature 1–2 years earlier than those of Asian origin.[9] Despite geographic differences, there are no differences in physiologic and pharmacologic parameter values that impact the use of Asian or Mauritian cynomolgus monkeys for nonclinical safety assessments.[10]

The cynomolgus monkey has become the most used NHP for biomedical research and nonclinical safety assessments since the Indian government banned the export of rhesus monkeys in 1978.[11] Background information, including the body weight and clinical pathology reference intervals (RIs), has been reported in the literature and appears to vary with the geographic origins of animals and by different laboratory environments.[12–17] These RIs were derived from a small number of animals, limited age ranges, and/or mixed genders.[12,15,17–20] In the current study, we provide RIs for 2 to <3 and 3 to <4 years of age and summarize age- and sex-related changes in clinical pathology analytes (4 different age groups) and body weights (9 different age groups) in cynomolgus monkeys of Mauritian origin used in nonclinical safety assessment in Pfizer Drug Safety Research & Development laboratories over a period of 5 years (2016–2020).

2 | MATERIALS AND METHODS

2.1 | Animals and husbandry

During this 5-year period, we had a dataset of 1823 monkeys. All animals were of Mauritian origin with a specific-pathogen-free status to exclude cercopithecine herpesvirus 1, simian beta-retrovirus 1–5, simian T-lymphotropic virus, simian immunodeficiency virus, and *Mycobacterium tuberculosis*. The animals were housed in the Association for Assessment and Accreditation of Laboratory Animal Care accredited facilities in Mauritius and the United States. To ensure suitable health status, physical examinations were conducted, body weights measured, and blood samples collected for hematologic and serum biochemistry analyte screens prior to the pre-study group allocation. All procedures performed on animals were in accordance with regulations and established guidelines and were reviewed and approved by an Institutional Animal Care and Use Committee. Clinically acceptable animals were allocated to study groups using a computer-assisted randomization procedure based on pre-study body weights.

2.2 | Body weight

Of the 1823 cynomolgus monkeys in this dataset, 1819 animals (960 males and 859 females) had pre-study age and body weight data. Animal body weights were taken during the acclimation periods right before the animals were assigned to study groups. If more than one body weight was measured, the last pre-study body weight immediately before the study started was used.

2.3 | Blood collection and analysis

Of the 1823 cynomolgus monkeys in this dataset, 1664 animals (860 males and 804 females) had both age and clinical pathology analyte data recorded. The clinical pathology data included hematologic, coagulation, and serum biochemical analytes. Table 1 lists analytes with the abbreviations, units, platforms, and/or methods. Also included in this table is an equivalency factor (%) of the expected biological variability, based on historical knowledge of the more common analytes (considered major and bolded in the table) for comparison purposes. All blood samples included were collected pre-study from animals that had been fasted overnight (approximately 12–18 hours) and before dosing started. If blood was collected more than once, the clinical pathology analyte values included were from the last blood collection before the study started. These blood samples were acquired by venipuncture of the femoral vein without anesthesia. Blood for hematology was collected into a tube with K2EDTA anticoagulant, and a blood smear was made. The whole-blood sample was kept at room temperature (15–25°C) if it was analyzed within 8 hours of collection. If the samples were not analyzed at this time, they were refrigerated (2–8°C) for analysis on an ADVIA 2120i/120 analyzer (Siemens). Blood for coagulation was collected into a tube with 3.2% sodium citrate and centrifuged at approximately 2700 relative centrifugal force for 10 minutes. The plasma was kept at room temperature if it was to be analyzed within 4 hours of receipt or frozen at −80°C for processing on the STA-R Evolution coagulation analyzer (Diagnostica Stago). Blood for serum biochemical

TABLE 1 Hematologic, coagulation, and serum biochemical analytes, analytic methods, and equivalency values for the common (major) analytes used in the cynomolgus monkey

Hematologic analytes	Abbreviation	Units	Platform	Equivalency value (%)
Red blood cells	RBC	$\times 10^6/\mu L$	ADVIA 2120/120	10
Hemoglobin	HGB	g/dL	ADVIA 2120/120	10
Hematocrit	HCT	%	ADVIA 2120/120	10
Mean corpuscular volume	MCV	fL	ADVIA 2120/120	
Mean corpuscular hemoglobin	MCH	pg	ADVIA 2120/120	
Mean corpuscular hemoglobin concentration	MCHC	g/dL	ADVIA 2120/120	
Red cell distribution width	RDW	%	ADVIA 2120/120	
Platelets	PLT	$\times 10^3/\mu L$	ADVIA 2120/120	25
Mean platelet volume	MPV	fL	ADVIA 2120/120	
White blood cells	WBC	$\times 10^3/\mu L$	ADVIA 2120/120	25
Neutrophil, absolute	NEUT	$\times 10^3/\mu L$	ADVIA 2120/120 or Microscopy	25
Lymphocyte, absolute	LYM	$\times 10^3/\mu L$	ADVIA 2120/120 or Microscopy	25
Monocyte, absolute	MONO	$\times 10^3/\mu L$	ADVIA 2120/120 or Microscopy	50
Basophil, absolute	BASO	$\times 10^3/\mu L$	ADVIA 2120/120 or Microscopy	50
Eosinophil, absolute	EO	$\times 10^3/\mu L$	ADVIA 2120/120 or Microscopy	50
Large unstained cell, absolute	LUC	$\times 10^3/\mu L$	ADVIA 2120/120	50
Neutrophil percent	NEUT_P	%	ADVIA 2120/120 or Microscopy	
Lymphocyte, percent	LYM_P	%	ADVIA 2120/120 or Microscopy	
Monocyte, percent	MONO_P	%	ADVIA 2120/120 or Microscopy	
Basophil, percent	BASO_P	%	ADVIA 2120/120 or Microscopy	
Eosinophil, percent	EO_P	%	ADVIA 2120/120 or Microscopy	
Large unstained cell, percent	LUC_P	%	ADVIA 2120/120	
Reticulocytes, absolute	RETIC	$\times 10^3/\mu L$	Calculation	25
Coagulation analytes	**Abbreviation**	**Units**	**Platform**	
Prothrombin time	PT	Seconds	Diagnostica Stago	15
Activated partial thromboplastin time	APTT	Seconds	Diagnostica Stago	15
Fibrinogen	FIB	mg/dL	Diagnostica Stago	20
Serum biochemistry analytes	**Abbreviation**	**Units**	**Methodology**	
Creatinine	CREA	mg/dL	Kinetic Alkaline Picrate	20
Urea nitrogen	BUN	mg/dL	Urease	20
Aspartate aminotransferase	AST	U/L	Modified IFCC	30
Alanine aminotransferase	ALT	U/L	Modified IFCC	30
Gamma glutamyltransferase	GGT	U/L	Modified IFCC	20
Alkaline phosphatase	ALP	U/L	Modified IFCC	30
Total bilirubin	TBIL	mg/dL	Vanadate Oxidation	25
Bile acids	BILE_AC	µmol/L	Thio NAD	
Total protein	TP	g/dl	Biuret	15
Albumin	ALB	g/dL	BCG Dye Binding	15
Globulin	GLOB	g/dL	Calculated	15
Albumin/globulin ratio	AG		Calculated	
Glucose	GLUC	mg/dL	Hexokinase	20
Cholesterol	CHOL	mg/dL	Enzymatic	20

TABLE 1 (Continued)

Serum biochemistry analytes	Abbreviation	Units	Methodology	
Triglycerides	TRIG	mg/dL	Modified Trinder	25
Phosphorus	PHOS	mg/dL	Phosphomolybdate	20
Calcium	CA	mg/dL	Arsenazo III	10
Chloride	CL	mmol/L	Ion-Selective Electrode	5
Sodium	NA	mmol/L	Ion-Selective Electrode	5
Potassium	K	mmol/L	Ion-Selective Electrode	10
Amylase	AMYL	U/L	Ethylidene Blocked –pNPG7	
Lipase	LIP	U/L	Colorimetric Rate	
Insulin	INS	uIU/mL	Sandwich Immunoassay	
Magnesium	MG	mg/dL	Xylidyl Blue	
Thyroid stimulating hormone	TSH	µIU/mL	Competitive Immunoassay	
Total T3	T3	ug/dL	UPLC-MS/MS	
Total T4	T4	ug/dL	UPLC-MS/MS	
C-Reactive protein, high sensitivity	CRPHS	mg/L	Sandwich Immunoassay	

Note: Bold analytes are considered major analytes that were given equivalency factors as shown.

analysis was collected into a serum separator tube without anticoagulant and left standing at room temperature for 15 minutes prior to centrifugation at approximately 2700 relative centrifugal force for 10 minutes. Serum was refrigerated (2 to −8°C) for analysis on the day of collection or frozen at −80°C for processing on the ADVIA 1800 (Siemens) for most analytes, except for insulin (ADVIA Centaur XP; Siemens), TSH (Immunite 1000, Siemens), and T3 and T4 (UPLC-MS/MS, Agilent 1290 UPLC coupled to an AB Sciex 6500 triple quadrupole mass spectrometer).

2.4 | Study groups

For body weight comparisons, animals were grouped semi-yearly from 2 to <3 years of age and yearly from 3 to 10 years of age. Age groups and the number of animals per age group are presented in Figure 1. For hematologic, coagulation, and serum biochemical analyses, animals were grouped into the following 4 age categories: 2 to <3 years (111 males; 55 females), 3 to <4 years (435 males; 392 females), 4 to <5 years (165 males; 182 females), and 5 to 10 years (149 males; 175 females) of age for each sex. Body weight and clinical pathology comparisons were made by age group and between male and female animals.

2.5 | Statistical analysis

The differences in body weights among age groups and between sex were analyzed using the two-sided t test. Endpoints were assigned to each animal as the value corresponding to the measurement taken closest to the study start. Each value was then log-transformed to normalize the data.

The differences in mean clinical pathology analyte values among age groups and between sex groups were analyzed using

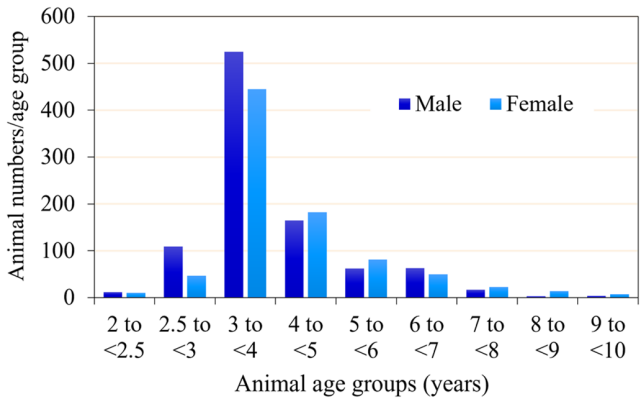

FIGURE 1 Animal numbers per age group. Of the 1819 animals (956 males and 863 females), the ages ranged from 2.2 to 9.6 years for males and 2.2 to 10 years for females. The mean age was 4.0 years for males and 4.3 years for females

equivalence testing (ie, two one-sided t tests, or TOST). For equivalence testing, a subjective equivalency factor or threshold was assigned to common or major (as defined in the blood collection and analysis section) analytes, based on the expected biological equivalence or variation range of individual analytes in Mauritian cynomolgus monkeys (Table 1). The thresholds were specified in percentages predetermined for a set of relevant analyte values and used to specify upper and lower equivalence bounds. Differences that did not fall inside the equivalence bounds suggested biologically meaningful differences. For each analyte, an equivalence test was run on every pair of the different age groups using the R package TOSTER.[21] Each test generated an accompanying graph that contained a 90% confidence interval. In addition,

a Kolmogorov–Smirnov test was run to test the difference in the distribution, and an empirical cumulative distribution function graph was created. Values that were not equivalent had a *P*-value of <0.05 and appeared to be outside of normal biological variation were included and discussed in the results.

The other hematologic analytes (mean cell volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], red blood cell distribution width [RDW], mean platelet volume [MPV], and white blood cell percentages) and serum biochemistry analytes (bile acid, amylase, lipase, insulin, TSH, T3, T4, high sensitivity C-reactive protein, and magnesium) were considered minor analytes. There were fewer numbers of historical controls or background data for some of these analytes in our facility and some of these analytes are not as relevant in nonclinical toxicity studies, so we were unable to create equivalency values. Thus, we did not include these analytes in the statistical analysis regarding age- or sex-related differences.

The RI calculations were conducted separately for each sex. Outliers were first identified for each analyte in each age group and removed.[22] For parameters with sample sizes of $n > 120$ after the outlier removal, the nonparametric method was used for the RI by calculating the 2.5th and 97.5th percentiles as the lower and upper reference limits, respectively. For $20 \le n \le 120$, when a parameter was normally distributed (ie, when the normality test *P*-value was >0.3 on either the raw or logarithmic scale), the parametric method was used; when normality did not hold (ie, when the normality test *P*-value was ≤0.3), a robust method was used.[23] RIs were calculated for all (major and minor) parameters as long as all sample sizes were $n > 40$. When the final sample size was less than 20, only descriptive statistics were reported. For a few parameters, only one animal was available per sex, and thus no statistics were included. The RI calculations were conducted using the R package RIs. The 95% coverage criterion was used for all the methods, and 90% confidence intervals were calculated for the lower and upper RIs. All the RI calculations were conducted by age group, which were divided into 2 to <3 years and 3 to <4 years of age.

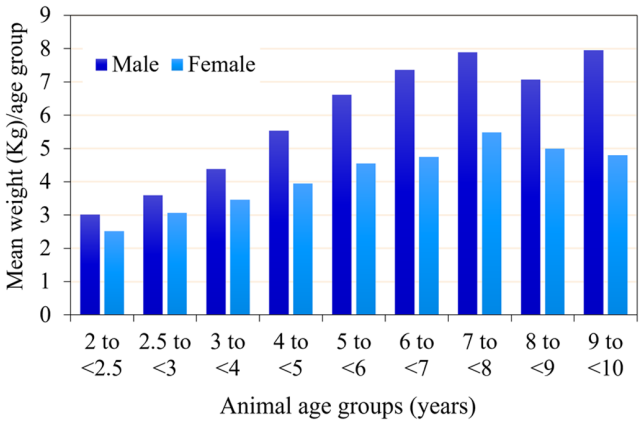

FIGURE 2 Animal body weights (kg) per age group. The group mean body weights were statistically higher ($P < 0.01$) in males than females for all age groups from 2 to 10 years. Body weights peaked at 7 to 8 years of age in both males (7.9 kg) and females (5.5 kg)

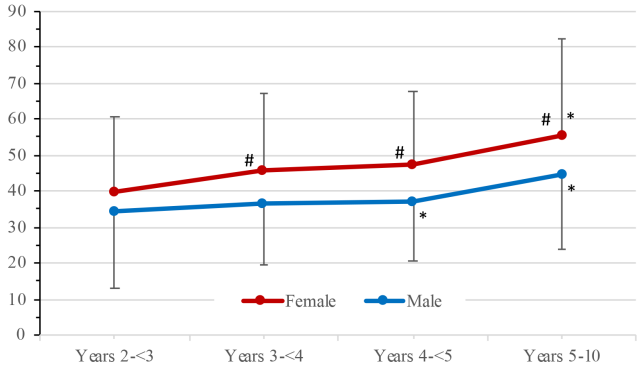

FIGURE 3 The sex- and age-related differences in reticulocyte (RETIC) counts. The group mean RETIC counts were statistically higher (#) in females than males in the 3 to 10 years of age groups. In females, the group mean RETIC counts were statistically higher (*) in animals 5 to 10 years of age than in those 2 to <4 years of age. In males, the group mean RETIC counts were statistically higher (*) in animals 4 to 10 years of age than in those 2 to <4 years of age

3 | RESULTS

3.1 | Age- and sex-related changes in body weights

Body weights per age group are presented in Figure 2. A total of 1819 animals ranged in age from 2.2 to 9.6 years for males ($n = 960$ or 52.8%) and 2.2 to 12.4 years for females ($n = 859$ or 47.2%). The mean age was 4.0 years for males and 4.3 years for females. Body weights were statistically higher ($P < 0.01$) in males than in females in all age groups from 2 to 10 years (Figure 2), suggesting that sexual dimorphism in body weights begins as early as 2 years of age. The sexual dimorphism in body weights became prominent after 4 years of age. Body weights reached peak values at 7 to 8 years of age in both males (7.9 kg) and females (5.5 kg), with a 2.4 kg difference in the peak mean body weights.

3.2 | Sex-related changes in hematologic, coagulation, and serum biochemistry analytes

Sex-related mean hematologic differences were limited to higher reticulocyte (RETIC) counts in females than males in some age groups. As shown in Figure 3, the RETIC index trended higher in females than males, and females had statistically higher RETIC indices than males from 3 to 10 years of age. There were no sex-related changes in the mean coagulation analytes.

Sex-related mean serum biochemistry differences included higher ALP and GGT activities in males than females in all age groups, as well as higher creatinine concentrations in males than females and higher triglyceride and cholesterol concentrations in females than males in some age groups. As shown in Figures 5 to 7, males had statistically higher ALP activity, GGT activity, and

creatinine levels (from 2 to 10 years, 2 to 10 years, and 5 to 10 years of age, respectively) than females of the same age groups. Females had statistically higher triglyceride levels than males from 4 to 10 years of age, as shown in Figure 8. As shown in Figure 9, the cholesterol concentration trended higher in females than males, and females had statistically higher cholesterol levels than males from 5 to 10 years of age.

Sex-related changes occurred in mean hematologic and serum biochemistry analyte values. Higher ALP and GGT activities were seen in males compared with females from 2 to 10 years of age, higher RETIC values were seen in females compared with males from 3 to 10 years of age, higher triglyceride concentrations were seen in females than males from 4 to 10 years of age, and higher creatinine concentrations were seen in males than females and higher cholesterol concentrations were seen in females compared with males from 5 to 10 years of age.

3.3 | Age-related changes in hematologic, coagulation, and serum biochemistry analytes

Age-related mean hematologic differences were observed in some age groups and included higher RETIC counts and lower lymphocyte counts in both sexes. As shown in Figure 3, RETIC values generally increased with age and were statistically higher in males 4 to 10 years of age and females 5 to 10 years of age (vs males and females 2 to <4 years of age). As shown in Figure 4, lymphocyte counts were comparable from 2 to 5 years of age but were statistically lower in males and females 5 to 10 years of age (vs males 4 to <5 years of age and females 2 to <3 years of age, respectively). There were no age-related changes in mean coagulation analytes

Age-related differences in mean serum biochemistry analytes were observed in some age groups. These included lower ALP and GGT activities, and phosphorus and globulin concentrations in both sexes, as well as higher creatinine concentrations in males and triglyceride concentrations in females. As shown in Figures 5 and 6, ALP and GGT activities generally decreased with age; there were statistically significant decreases in ALP activity in males and females 3 to

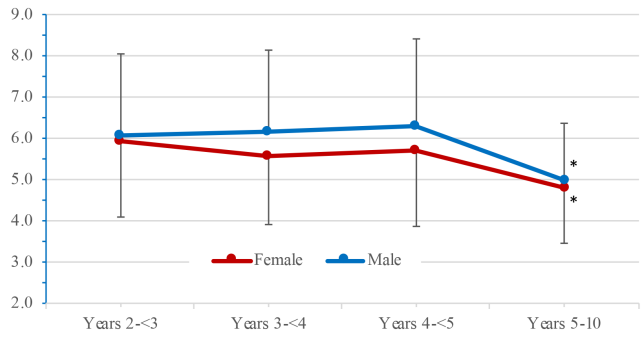

FIGURE 4 The age-related differences in lymphocyte counts. The group mean lymphocyte counts were statistically lower (*) in male and female animals 5 to 10 years of age than in those 4 to <5 and 2 to <3 years of age, respectively

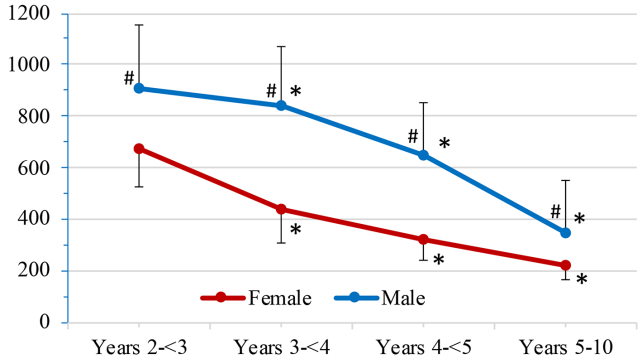

FIGURE 5 The sex- and age-related differences in alkaline phosphatase (ALP) activity. The group mean ALP activity was statistically higher (#) in males than females for all age groups 2 to 10 years. In males and females, the group mean ALP activity was statistically lower (*) in animals 3 to 10 years of age than in those 2 to <3 years of age

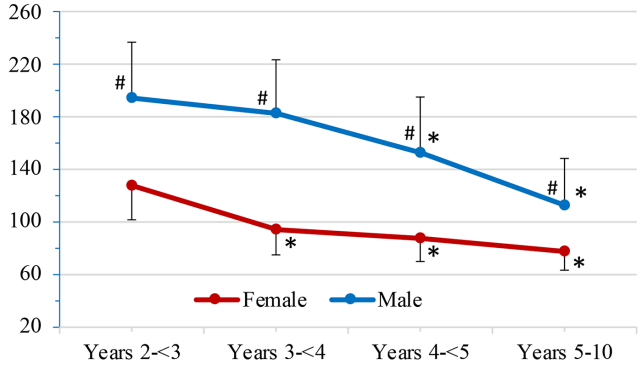

FIGURE 6 The sex- and age-related differences in gamma-glutamyl transferase (GGT) activity. The group mean GGT activity was statistically higher (#) in males than females for all age groups 2 to 10 years. In males, the group mean GGT activity was statistically lower (*) in animals 4 to 10 years of age than in those 2 to <4 years of age. In females, the group mean GGT activity was statistically lower (*) in animals 3 to 10 years than in those 2 to <3 years of age.

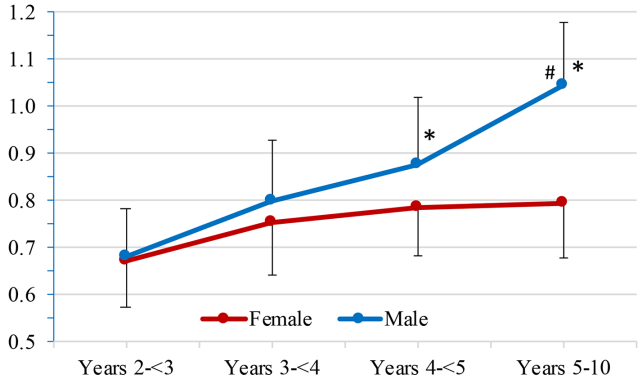

FIGURE 7 The sex- and age-related differences in serum creatinine concentration. The group mean creatinine concentration was statistically higher (#) in males than females in the 5 to 10 years of age group. In males, the group mean creatinine concentration was statistically higher (*) in animals 4 to 10 years of age than in those 2 to <4 years of age

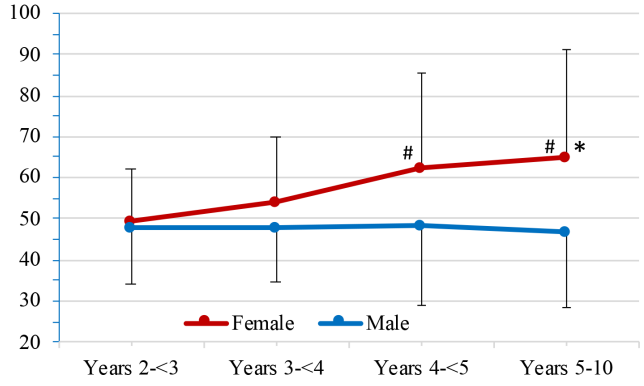

FIGURE 8 The sex- and age-related differences in serum triglyceride concentration. The group mean triglyceride concentration was statistically higher (#) in females than males in the 4 to 10 years of age groups. In females, the group mean triglyceride concentration was statistically higher (*) in animals 5 to 10 years of age than in those 2 to <3 years of age

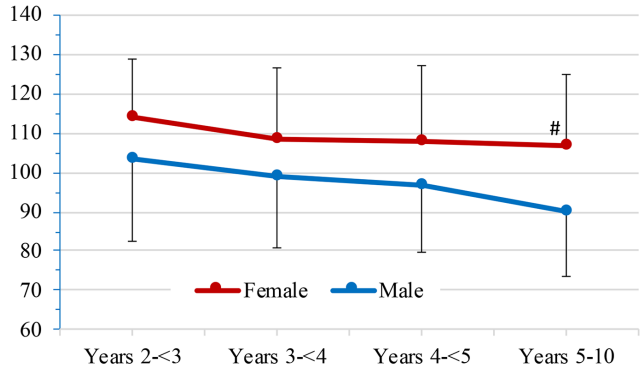

FIGURE 9 The sex-related differences in serum cholesterol concentration. The group mean cholesterol concentration was statistically higher (#) in females than males in the 5 to 10 years of age group

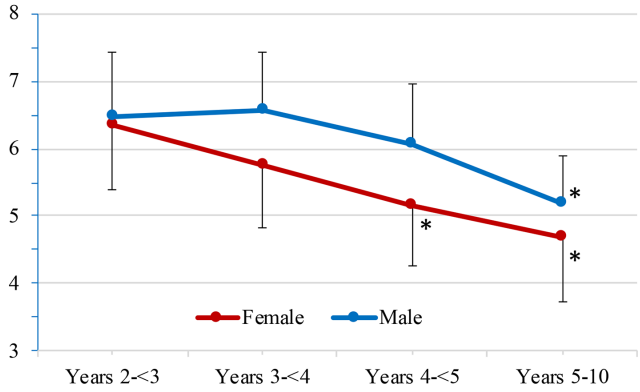

FIGURE 10 The age-related differences in serum phosphorus concentration. In males, the group mean serum phosphorus concentration was statistically lower (*) in animals 5 to 10 years of age than in those 2 to <4 years of age. In females, the group mean serum phosphorus concentration was statistically lower (*) in animals 4 to 10 years of age than in those 2 to <4 years of age

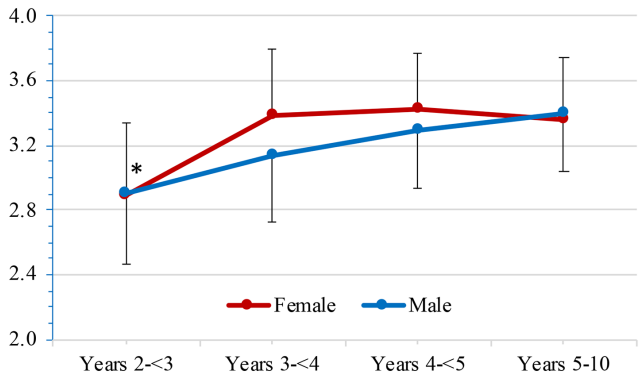

FIGURE 11 The age-related differences in serum globulin concentration. The group mean globulin concentration was statistically lower (*) in males and females 2 to <3 years of age than in those 3 to 10 years of age

10 years of age (vs males and females 2 to <3 years of age) and statistically significant decreases in GGT activity in males 4 to 10 years of age and females 3 to 10 years of age (vs males 2 to <4 years of age and females 2 to <3 years of age, respectively). As shown in Figure 7, statistically significant age-related increases in creatinine concentrations were seen in males 4 to 10 years of age (vs males 2 to <4 years of age). Statistically significant increases in triglyceride concentrations were seen in females 5 to 10 years of age (vs females 2 to <3 years of age), as shown in Figure 8. There were statistically significant decreases in phosphorus concentrations in males 5 to 10 years of age and females 4 to 10 years of age (vs males and females 2 to <4 years of age), as shown in Figure 10. As shown in Figure 11, statistically significant lower globulin concentrations were found in males and females 2 to <3 years of age (vs. males and females 3 to 10 years of age).

Age-related changes were seen in mean hematologic and serum biochemical analytes. Globulin concentrations were lower in both sexes 2 to <3 years of age compared to older animals. ALP activity was lower in both sexes 3 to 10 years of age compared with younger animals. GGT activity was lower in males 4 to 10 years of age and females 3 to 10 years of age compared with younger males and females. Creatinine concentrations were higher in males 4 to 10 years of age compared with younger males. Phosphorus concentrations were lower in males 5 to 10 years of age and females 4 to 10 years of age compared with younger males and females. RETIC values were higher in males 4 to 10 years of age and females 5 to 10 years of age compared with younger males and females. Triglyceride values were higher in females 5 to 10 years of age compared with younger females. Finally, lymphocyte numbers were lower in both sexes at 5 to 10 years of age compared with younger animals.

3.4 | Hematologic, coagulation, and serum biochemical reference intervals.

RIs for clinical pathology analytes for the 2 to <3 years of age and 3 to <4 years of age groups were provided since these are the most typical age groups used in nonclinical safety studies (Tables 2 to 7).

TABLE 2 Reference intervals of hematologic analytes for 2- to <3-year-old cynomolgus monkeys

		Descriptive statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Min	Max	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
RBC	M	111	110	6.82	0.43	6.85	5.76	7.9	5.97	7.66	(5.86, 6.09)	(7.55, 7.78)
RBC	F	54	52	6.58	0.47	6.63	5.52	7.53	5.65	7.5	(5.47, 5.84)	(7.31, 7.68)
HGB	M	111	109	13.44	0.62	13.4	11.9	14.9	12.23	14.66	(12.06, 12.39)	(14.49, 14.83)
HGB	F	54	53	13.00	0.86	13	11.4	14.7	11.31	14.68	(10.98, 11.65)	(14.35, 15.01)
HCT	M	111	109	46.29	1.96	46.4	41.6	50.1	42.42	50.25	(41.91, 42.96)	(49.78, 50.77)
HCT	F	54	52	45.37	2.92	45.05	39.5	51.6	39.65	51.09	(38.51, 40.78)	(49.95, 52.23)
MCV	M	111	108	67.85	2.97	67.9	60.7	74.3	62.03	73.68	(61.22, 62.83)	(72.87, 74.48)
MCV	F	54	49	68.18	2.24	68.3	63.7	72.9	63.79	72.57	(62.90, 64.69)	(71.67, 73.47)
MCH	M	111	107	19.73	0.93	19.8	17.5	22	17.91	21.55	(17.66, 18.16)	(21.30, 21.80)
MCH	F	54	52	19.49	0.81	19.5	18	21.4	17.92	21.07	(17.60, 18.23)	(20.76, 21.39)
MCHC	M	111	106	29.01	0.86	28.9	27.3	31.2	27.24	30.7	(27.00, 27.45)	(30.45, 30.96)
MCHC	F	54	52	28.56	0.82	28.65	26.8	30.3	26.95	30.18	(26.62, 27.27)	(29.86, 30.50)
RDW	M	111	110	14.28	0.97	14.1	12	16.5	12.27	16.22	(12.01, 12.50)	(15.96, 16.54)
RDW	F	54	54	14.18	0.98	14.25	12.5	16.4	12.25	16.11	(11.88, 12.63)	(15.73, 16.48)
PLT	M	111	104	368.54	52.72	364	235	501	265.21	471.87	(250.68, 279.74)	(457.33, 486.40)
PLT	F	54	50	393.84	62.11	391.5	274	548	272.1	515.58	(247.41, 296.79)	(490.89, 540.27)
MPV	M	111	109	8.73	1.09	8.5	7	11.4	6.39	10.83	(6.09, 6.64)	(10.48, 11.20)
MPV	F	54	51	8.69	0.92	8.6	7	10.7	6.71	10.46	(6.35, 6.99)	(10.02, 10.85)
WBC	M	111	105	11.48	2.86	11.5	6.4	19.2	5.66	17.06	(4.91, 6.39)	(16.29, 17.91)
WBC	F	54	49	11.05	2.29	10.8	6.1	15.9	6.56	15.53	(5.64, 7.48)	(14.61, 16.45)
NEUT	M	111	106	4.79	2.49	4.32	1.19	11.29	BFA	9.47	BFA	(8.66, 10.31)
NEUT	F	54	49	4.43	1.51	4.19	2.36	8.11	1.11	7.34	(0.55, 1.79)	(6.61, 8.13)
LYM	M	111	107	5.87	1.68	5.82	2.21	10.14	2.57	9.17	(2.11, 3.03)	(8.71, 9.63)
LYM	F	54	52	5.74	1.59	5.59	2.81	9.28	2.63	8.85	(2.01, 3.25)	(8.23, 9.47)
MONO	M	111	106	0.37	0.12	0.35	0.15	0.67	0.12	0.59	(0.09, 0.15)	(0.55, 0.63)
MONO	F	54	52	0.40	0.14	0.39	0.16	0.74	0.09	0.68	(0.04, 0.14)	(0.62, 0.75)
BASO	M	111	106	0.03	0.01	0.03	0.01	0.06	0	0.06	(0.00, 0.01)	(0.06, 0.06)
BASO	F	54	50	0.03	0.01	0.03	0.01	0.06	0.01	0.06	(0.00, 0.01)	(0.05, 0.06)
EO	M	111	104	0.18	0.14	0.15	0.01	0.56	BFA	0.44	BFA	(0.39, 0.50)

(Continues)

TABLE 2 (Continued)

		Descriptive statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Min	Max	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
EO	F	54	50	0.17	0.13	0.13	0.02	0.46	BFA	0.42	BFA	(0.35, 0.50)
LUC	M	111	105	0.10	0.05	0.1	0.02	0.21	0.01	0.19	BFA	(0.18, 0.20)
LUC	F	54	51	0.10	0.03	0.09	0.04	0.18	0.02	0.16	(0.01, 0.03)	(0.15, 0.18)
NEUT_P	M	111	111	41.12	15.77	40.85	13.97	77.83	8.96	71.81	(5.26, 12.34)	(67.47, 76.12)
NEUT_P	F	54	52	41.40	11.81	40.92	18.09	68.84	18.26	64.54	(13.66, 22.86)	(59.94, 69.14)
LYM_P	M	111	111	52.22	14.36	53.03	20.33	78.59	24.03	81.34	(20.11, 27.75)	(78.02, 84.77)
LYM_P	F	54	52	51.79	10.64	52.12	25.79	71.23	30.38	73.62	(26.58, 35.20)	(69.26, 77.24)
MONO_P	M	111	109	3.27	0.92	3.10	1.45	5.47	1.35	5.07	(1.11, 1.55)	(4.81, 5.39)
MONO_P	F	54	52	3.39	1.01	3.40	1.59	5.36	1.34	5.43	(0.99, 1.68)	(5.07, 5.78)
BASO_P	M	111	109	0.27	0.08	0.28	0.08	0.47	0.11	0.44	(0.09, 0.14)	(0.42, 0.47)
BASO_P	F	54	51	0.28	0.08	0.28	0.11	0.48	0.12	0.44	(0.09, 0.15)	(0.41, 0.47)
EO_P	M	111	104	1.62	1.31	1.21	0.07	5.41	BFA	4.07	BFA	(3.55, 4.65)
EO_P	F	54	52	1.61	1.21	1.24	0.14	4.37	BFA	3.8	BFA	(3.02, 4.45)
LUC_P	M	111	105	0.89	0.37	0.89	0.20	1.71	0.15	1.62	(0.06, 0.24)	(1.52, 1.72)
LUC_P	F	54	52	0.87	0.25	0.85	0.30	1.30	0.37	1.36	(0.27, 0.47)	(1.26, 1.46)
RETIC	M	111	105	31.07	12.64	29	12	67	4.49	55.57	(1.27, 7.79)	(51.53, 60.05)
RETIC	F	54	48	33.42	12.43	32	15	65	6.53	57.46	(1.96, 12.52)	(51.40, 63.45)

Note: See Table 1 for abbreviations of individual analytes.

Abbreviations: BFA, beyond the feasibility of analysis; CI, confidence interval; F, female; LRI, lower reference limit; M, male; N, animal number/sample size; RI, reference interval; SD, standard deviation; URI, upper reference limit.

TABLE 3 Reference intervals of hematologic analytes for 3- to <4-year-old cynomolgus monkeys

		Descriptive statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Min	Max	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
RBC	M	435	429	6.77	0.41	6.75	5.65	7.83	6.05	7.6	(5.98, 6.10)	(7.54, 7.75)
RBC	F	392	388	6.47	0.49	6.47	5.13	7.83	5.5	7.45	(5.35, 5.64)	(7.31, 7.55)
HGB	M	435	434	13.63	0.74	13.6	11.6	15.7	12.29	15.1	(12.10, 12.40)	(15.00, 15.20)
HGB	F	392	388	12.88	0.78	12.9	10.7	15.1	11.2	14.33	(11.10, 11.40)	(14.10, 14.40)
HCT	M	435	434	46.4	2.7	46.3	39.7	53.3	41.2	51.7	(41.0, 41.9)	(51.1, 52.5)
HCT	F	392	388	44.8	2.9	44.8	36.5	52.9	39.3	50.5	(38.1, 39.8)	(49.9, 51.2)
MCV	M	435	432	68.6	3.5	68.5	58.5	78.8	61.7	75.7	(61.0, 62.4)	(74.8, 76.7)
MCV	F	392	390	69.1	3.8	69.1	58.8	79.4	61.1	77.5	(59.4, 62.5)	(76.3, 78.1)
MCH	M	435	432	20.2	1.1	20.1	17.1	23	18	22.3	(17.9, 18.2)	(22.0, 22.6)
MCH	F	392	387	19.9	1.1	19.9	17.1	22.8	17.8	21.9	(17.5, 18.1)	(21.8, 22.4)
MCHC	M	435	433	29.4	1.2	29.4	26.2	32.7	27.1	31.7	(26.8, 27.4)	(31.5, 32.0)
MCHC	F	392	388	28.8	1.1	28.8	25.9	31.9	26.6	30.9	(26.3, 26.8)	(30.8, 31.4)
RDW	M	435	432	14.29	0.95	14.25	12	17	12.58	16.2	(12.30, 12.70)	(16.00, 16.40)
RDW	F	392	388	14.11	0.99	14.1	11.2	16.7	12.27	16.1	(12.20, 12.50)	(15.90, 16.30)
PLT	M	434	431	383	71	379	200	579	246	523	(237, 258)	(508, 534)
PLT	F	389	385	409	79	400	232	630	256	574	(245, 269)	(559, 601)
MPV	M	434	427	8.7	1.1	8.5	6	11.9	6.9	11.1	(6.7, 7.0)	(11.0, 11.5)
MPV	F	389	382	8.8	1.2	8.8	5.9	12.1	6.8	11.6	(6.4, 7.2)	(11.1, 11.9)
WBC	M	427	420	12.3	3.2	12.1	5.5	21.8	7.1	20.1	(6.7, 7.4)	(18.5, 21.1)
WBC	F	392	387	12.3	3.4	11.8	3.8	22	6.8	19.9	(6.0, 7.3)	(18.6, 20.7)
NEUT	M	435	419	5.1	2.5	4.5	0.9	12.6	1.6	10.8	(1.3, 1.8)	(10.2, 12.0)
NEUT	F	392	385	5.8	3	5.1	1.1	14.4	1.7	12.8	(1.3, 2.0)	(12.2, 13.5)
LYM	M	435	430	6.1	1.8	5.8	1.9	11.4	2.9	10.2	(2.6, 3.1)	(9.6, 10.7)
LYM	F	392	391	5.6	1.6	5.3	2.2	10	3	9.3	(2.4, 3.2)	(9.0, 9.5)
MONO	M	435	419	0.4	0.14	0.38	0.12	0.82	0.18	0.74	(0.17, 0.20)	(0.68, 0.78)
MONO	F	392	381	0.42	0.15	0.41	0.1	0.88	0.18	0.77	(0.16, 0.20)	(0.72, 0.79)
BASO	M	435	424	0.035	0.016	0.03	0	0.08	0.01	0.07	(0.01, 0.01)	(0.07, 0.08)
BASO	F	392	379	0.035	0.014	0.03	0.01	0.07	0.01	0.07	(0.01, 0.01)	(0.06, 0.07)
EO	M	435	409	0.22	0.18	0.17	0.01	0.81	0.02	0.67	(0.02, 0.03)	(0.62, 0.78)
EO	F	392	369	0.3	0.2	0.2	0	0.9	0	0.8	(0.0, 0.0)	(0.8, 0.9)

(Continues)

TABLE 3 (Continued)

		Descriptive statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Min	Max	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
LUC	M	435	424	0.105	0.043	0.1	0.02	0.23	0.04	0.21	(0.03, 0.04)	(0.20, 0.22)
LUC	F	392	384	0.108	0.045	0.1	0.02	0.23	0.04	0.21	(0.04, 0.05)	(0.19, 0.22)
NEUT_P	M	435	419	55	27	48	9	135	17	116	(14, 19)	(110, 129)
NEUT_P	F	392	385	62	32	55	12	155	19	138	(14, 21)	(131, 145)
LYM_P	M	435	430	65	20	63	20	123	31	109	(28, 33)	(103, 115)
LYM_P	F	392	391	60	17	57	23	107	32	100	(26, 34)	(97, 102)
MONO_P	M	435	419	4.4	1.5	4.1	1.3	8.8	1.9	8	(1.8, 2.1)	(7.3, 8.4)
MONO_P	F	392	381	4.5	1.6	4.4	1.1	9.5	1.9	8.3	(1.7, 2.1)	(7.7, 8.5)
BASO_P	M	435	424	0.38	0.17	0.32	0	0.86	0.11	0.75	(0.11, 0.11)	(0.75, 0.86)
BASO_P	F	392	379	0.37	0.15	0.32	0.11	0.75	0.11	0.75	(0.11, 0.11)	(0.65, 0.75)
EO_P	M	435	409	2.4	1.9	1.8	0.1	8.7	0.2	7.2	(0.2, 0.3)	(6.7, 8.4)
EO_P	F	392	369	2.9	2.2	2.3	0.2	9.8	0.5	8.7	(0.3, 0.5)	(8.2, 9.3)
LUC_P	M	435	424	1.13	0.46	1.08	0.22	2.47	0.43	2.26	(0.32, 0.43)	(2.15, 2.37)
LUC_P	F	392	384	1.16	0.49	1.08	0.22	2.47	0.43	2.26	(0.43, 0.54)	(2.04, 2.37)
RETIC	M	435	423	35	14	33	7	75	13	66	(13, 13)	(64, 73)
RETIC	F	392	380	44	18	42	12	98	14	86	(13, 18)	(79, 89)

Note: See Table 1 for abbreviations of individual analytes.

Abbreviations: CI, confidence interval; F, female; LRI, lower reference limit; M, male; N, animal number/sample size; RI, reference interval; SD, standard deviation; URI, upper reference limit.

TABLE 4 Reference intervals of coagulation analytes for 2- to <3-year-old cynomolgus monkeys

		Descriptive Statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Minimal	Maximal	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
PT	M	110	109	12.71	0.57	12.7	11.4	14	11.6	13.83	(11.44, 11.75)	(13.68, 13.99)
PT	F	53	52	12.39	0.51	12.4	11.4	13.5	11.39	13.39	(11.19, 11.59)	(13.19, 13.59)
APTT	M	110	108	22.29	1.23	22.2	19.3	24.9	19.76	24.67	(19.45, 20.07)	(24.32, 25.06)
APTT	F	53	52	21.73	1.05	21.75	19.4	23.8	19.67	23.78	(19.26, 20.08)	(23.37, 24.19)
FIB	M	110	104	189.14	23.64	186	130	245	142.81	235.48	(136.29, 149.32)	(228.97, 242.00)
FIB	F	53	51	176.08	17.95	174	140	214	140.9	211.25	(133.84, 147.97)	(204.19, 218.32)

Note: See Table 1 for abbreviations of individual analytes.

Abbreviations: CI, confidence interval; F, female; LRI, lower reference limit; M, male; N, animal number/sample size; RI, reference interval; SD, standard deviation; URI, upper reference limit.

TABLE 5 Reference intervals of coagulation analytes for 3- to <4-year-old cynomolgus monkeys

		Descriptive Statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Minimal	Maximal	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
PT	M	389	385	12.93	0.59	13	11.3	14.6	11.77	14.2	(11.6, 11.9)	(13.9, 14.4)
PT	F	377	369	12.71	0.54	12.7	11.3	14.2	11.7	13.9	(11.60, 11.8)	(13.70, 14.0)
APTT	M	390	383	22.4	1.4	22.2	19	26.2	20.2	25.5	(19.7, 20.4)	(25.2, 26.0)
APTT	F	377	366	22.2	1.3	22.2	19.2	25.8	19.9	25.1	(19.7, 20.1)	(24.6, 25.3)
FIB	M	390	383	195	26	193	129	265	151	247	(136, 154)	(241, 256)
FIB	F	377	367	182	26	181	115	249	129	236	(125, 130)	(232, 241)

Note: See Table 1 for abbreviations of individual analytes.

Abbreviations: CI, confidence interval; F, female; LRI, lower reference limit; M, male; N, animal number/sample size; RI, reference interval; SD, standard deviation; URI, upper reference limit.

TABLE 6 Reference intervals of serum biochemistry and other serum analytes for 2- to <3-year-old cynomolgus monkeys

		Descriptive Statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Min	Max	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
CREA	M	100	100	0.68	0.10	0.7	0.5	0.9	0.48	0.88	(0.45, 0.51)	(0.86, 0.91)
CREA	F	53	51	0.66	0.09	0.7	0.5	0.8	0.47	0.86	(0.43, 0.50)	(0.83, 0.88)
BUN	M	100	94	18.17	2.63	18	12	25	12.87	23.41	(12.18, 13.76)	(22.64, 24.14)
BUN	F	53	51	17.24	2.31	17	12	22	12.7	21.77	(11.79, 13.61)	(20.86, 22.68)
AST	M	100	98	44.49	8.54	44	26	64	27.76	61.22	(25.33, 30.18)	(58.80, 63.64)
AST	F	53	49	40.27	4.85	40	31	52	30.77	49.76	(28.82, 32.71)	(47.82, 51.71)
ALT	M	100	97	48.24	13.02	47	24	78	20.09	72.27	(16.44, 22.78)	(67.50, 76.18)
ALT	F	53	50	46.70	12.68	45	29	73	19.57	71.62	(15.37, 24.51)	(66.24, 77.98)
GGT	M	110	109	193.67	39.70	193	97	284	115.86	271.48	(105.17, 126.55)	(260.79, 282.17)
GGT	F	53	53	127.64	26.16	130	82	174	74.15	180.86	(64.57, 82.73)	(172.13, 191.02)
ALP	M	100	98	892.66	226.77	851.5	493	1436	415.93	1336.34	(358.09, 474.91)	(1265.03, 1417.81)
ALP	F	53	53	677.09	152.88	662	352	987	377.46	976.72	(318.43, 436.49)	(917.69, 1035.75)
TBIL	M	100	96	0.20	0.07	0.2	0.1	0.3	0.07	0.33	(0.06, 0.09)	(0.31, 0.35)
TBIL	F	53	50	0.23	0.09	0.2	0.1	0.4	0.05	0.41	(0.01, 0.09)	(0.37, 0.44)
BILE_AC	M	13	12	1.77	0.81	1.7	0.7	3.1	NA	NA	(NA, NA)	(NA, NA)
BILE_AC	F	5	4	2.70	2.40	1.9	0.8	6.2	NA	NA	(NA, NA)	(NA, NA)
TP	M	100	99	7.57	0.42	7.5	6.7	8.4	6.72	8.4	(6.60, 6.81)	(8.29, 8.53)
TP	F	53	53	7.42	0.48	7.4	6.6	8.5	6.42	8.36	(6.25, 6.59)	(8.16, 8.57)
ALB	M	100	98	4.66	0.21	4.7	4.2	5.1	4.24	5.11	(4.17, 4.31)	(5.06, 5.18)
ALB	F	53	52	4.55	0.19	4.5	4.2	4.9	4.14	4.95	(4.05, 4.20)	(4.88, 5.04)
GLOB	M	100	100	2.91	0.44	3	2	3.9	2.03	3.81	(1.89, 2.14)	(3.72, 3.94)
GLOB	F	53	52	2.84	0.40	2.85	2.2	3.7	2.01	3.65	(1.87, 2.17)	(3.50, 3.82)
AG	M	100	98	1.62	0.28	1.6	1.2	2.3	1.05	2.16	(0.99, 1.15)	(2.07, 2.26)
AG	F	53	51	1.61	0.23	1.6	1.1	2.1	1.16	2.05	(1.07, 1.25)	(1.96, 2.14)
GLUC	M	100	93	68.67	8.17	69	51	91	52.66	84.67	(50.28, 55.04)	(82.29, 87.05)
GLUC	F	53	51	77.59	12.09	78	54	102	53.89	101.28	(49.13, 58.65)	(96.53, 106.04)

TABLE 6 (Continued)

		Descriptive Statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Min	Max	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
CHOL	M	100	99	102.67	19.80	99	57	151	61.39	141.77	(56.02, 66.25)	(135.70, 149.02)
CHOL	F	53	50	113.02	13.01	112.5	84	141	87.52	138.52	(82.35, 92.69)	(133.35, 143.69)
TRIG	M	100	93	45.04	9.47	44	26	69	25.24	63.32	(22.57, 27.59)	(60.36, 66.53)
TRIG	F	53	51	47.82	11.32	48	26	71	25.64	70	(21.19, 30.10)	(65.55, 74.46)
PHOS	M	100	97	6.46	0.86	6.5	4.4	8.6	4.77	8.15	(4.52, 5.02)	(7.90, 8.39)
PHOS	F	53	51	6.23	0.82	6.1	4.5	7.8	4.58	7.94	(4.23, 4.89)	(7.65, 8.26)
CA	M	100	96	10.16	0.29	10.2	9.5	10.8	9.58	10.75	(9.47, 9.67)	(10.68, 10.83)
CA	F	53	53	10.04	0.37	10	9.3	10.7	9.29	10.79	(9.17, 9.42)	(10.66, 10.93)
CL	M	110	106	107.53	1.64	107	104	111	104.03	110.9	(103.52, 104.36)	(110.52, 111.47)
CL	F	53	52	108.40	1.75	108	105	112	104.78	112.07	(104.03, 105.37)	(111.46, 112.86)
NA	M	110	108	148.14	2.06	148	143	153	143.98	152.2	(143.46, 144.63)	(151.58, 152.73)
NA	F	53	52	146.81	1.77	146	143	150	142.64	150.55	(141.69, 143.08)	(149.94, 151.55)
K	M	110	103	4.23	0.32	4.2	3.5	5	3.57	4.86	(3.48, 3.66)	(4.76, 4.95)
K	F	53	48	4.26	0.29	4.25	3.7	4.9	3.63	4.82	(3.50, 3.71)	(4.68, 4.93)
AMYL	M	14	13	325.15	99.00	301	206	520	NA	NA	(NA, NA)	(NA, NA)
AMYL	F	1	1	NA	NA	NA	NA	NA	NA	NA	(NA, NA)	(NA, NA)
LIPASE	M	14	14	17.21	4.10	15	13	24	NA	NA	(NA, NA)	(NA, NA)
LIPASE	F	1	1	NA	NA	NA	NA	NA	NA	NA	(NA, NA)	(NA, NA)
CRPHS	M	15	14	1.20	0.52	1.15	0.3	1.9	NA	NA	(NA, NA)	(NA, NA)
CRPHS	F	10	9	1.07	0.77	0.8	0.2	2.6	NA	NA	(NA, NA)	(NA, NA)

Note: See Table 1 for abbreviations of individual analytes.

Abbreviations: CI, confidence interval; F, female; LRI, lower reference limit; M, male; N, animal number/sample size; NA, not applicable; RI, reference interval; SD, standard deviation; URI, upper reference limit.

TABLE 7 Reference intervals of serum biochemistry and other serum analytes for 3- to <4-year-old cynomolgus monkeys

		Descriptive statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Min	Max	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
CREA	M	322	319	0.79	0.13	0.8	0.5	1.1	0.6	1	(0.50, 0.60)	(1.00, 1.10)
CREA	F	303	300	0.75	0.11	0.8	0.5	1	0.6	1	(0.50, 0.60)	(0.90, 1.00)
BUN	M	322	317	18.4	2.5	18	12	25	14	23.1	(13.0, 14.0)	(23.0, 25.0)
BUN	F	303	291	18.3	2.5	18	11	25	14	23.7	(13.0, 15.0)	(23.0, 24.0)
AST	M	322	321	39.7	8	39	20	61	26	57	(25.0, 28.0)	(55.0, 59.0)
AST	F	303	295	35.6	6.7	35	20	54	23.4	49.6	(21.0, 25.0)	(48.0, 54.0)
ALT	M	322	310	42	12	40	19	79	21	68	(19, 22)	(64, 75)
ALT	F	303	283	46	16	42	19	98	22	86	(19, 25)	(80, 97)
GGT	M	403	396	178	38	174	94	286	106	263	(100, 117)	(253, 273)
GGT	F	379	373	93	17	91	53	143	64	130	(61, 67)	(128, 134)
ALP	M	322	319	824	215	797	396	1393	467	1310	(420, 490)	(1267, 1375)
ALP	F	303	298	426	113	410	191	735	237	670	(214, 256)	(630, 711)
TBIL	M	322	308	0.19	0.063	0.2	0.1	0.3	0.1	0.3	(0.100, 0.100)	(0.300, 0.300)
TBIL	F	301	278	0.181	0.063	0.2	0.1	0.3	0.1	0.3	(0.100, 0.100)	(0.300, 0.300)
BILE_AC	M	93	84	2.5	1.5	2.4	0.4	6.5	BFA	5.4	BFA	(4.9, 5.9)
BILE_AC	F	87	79	2.8	1.5	2.5	0.4	6.9	BFA	5.7	BFA	(5.2, 6.3)
TP	M	322	319	7.8	0.46	7.8	6.6	8.9	6.8	8.6	(6.70, 7.00)	(8.60, 8.70)
TP	F	303	301	7.85	0.42	7.9	6.7	8.9	6.9	8.6	(6.70, 7.00)	(8.50, 8.80)
ALB	M	322	314	4.65	0.21	4.65	4.1	5.2	4.2	5.1	(4.20, 4.30)	(5.00, 5.20)
ALB	F	303	302	4.47	0.22	4.5	4	5	4	4.9	(4.00, 4.10)	(4.90, 5.00)
GLOB	M	322	322	3.12	0.41	3.2	2.1	4	2.3	3.9	(2.10, 2.30)	(3.80, 3.90)
GLOB	F	303	303	3.37	0.41	3.4	2.3	4.5	2.4	4.1	(2.40, 2.60)	(4.00, 4.30)
AG	M	309	303	1.5	0.21	1.5	1.1	2	1.2	2	(1.20, 1.20)	(2.00, 2.00)
AG	F	297	293	1.34	0.19	1.3	1	1.8	1.04	1.8	(1.00, 1.10)	(1.70, 1.80)
GLUC	M	322	315	76	14	73	40	114	53	109	(51, 56)	(106, 112)
GLUC	F	303	298	82	19	80	43	130	52	122	(48, 55)	(118, 128)
CHOL	M	322	316	98	16	97	55	141	65	130	(61, 71)	(127, 132)
CHOL	F	303	302	107	17	108	71	154	74	142	(72, 79)	(137, 146)
TRIG	M	322	315	46	11	45	23	74	28	71	(25, 30)	(68, 72)
TRIG	F	303	296	52	14	50	21	91	29	82	(24, 31)	(78, 88)

TABLE 7 (Continued)

		Descriptive statistics							Reference interval (RI) and confidence interval (CI)			
Analyte	Sex	Initial N	Final N	Mean	SD	Median	Min	Max	LRL of RI (2.5%)	URL of RI (2.5%)	CI 90% of LRL	CI 90% of URL
PHOS	M	322	318	6.49	0.82	6.4	4.4	8.7	4.9	8.1	(4.80, 5.00)	(8.00, 8.20)
PHOS	F	303	299	5.65	0.85	5.6	3.6	7.8	3.9	7.4	(3.70, 4.00)	(7.10, 7.70)
CA	M	322	319	10.21	0.38	10.2	9.3	11.2	9.5	11	(9.40, 9.60)	(10.90, 11.10)
CA	F	303	301	10.08	0.38	10.1	9.2	11.1	9.4	10.95	(9.20, 9.50)	(10.80, 11.00)
CL	M	403	394	107.4	1.9	107	103	112	104	111	(103.0, 104.0)	(111.0, 112.0)
CL	F	379	374	108.7	2.1	109	103	114	105	113	(105.0, 106.0)	(113.0, 113.0)
NA	M	403	398	148.2	2.1	148	143	154	145	153	(144.0, 145.0)	(153.0, 154.0)
NA	F	379	373	147.4	2	147	143	153	144	152	(143.0, 144.0)	(151.0, 152.0)
K	M	403	391	4.28	0.33	4.3	3.4	5.2	3.7	5	(3.60, 3.80)	(4.90, 5.10)
K	F	379	377	4.4	0.4	4.3	3.2	5.5	3.6	5.2	(3.6, 3.7)	(5.2, 5.3)
AMYL	M	83	79	355	100	330	204	608	122	535	(89, 152)	(492, 577)
AMYL	F	84	82	349	97	338	206	589	141	535	(113, 168)	(498, 568)
LIP	M	83	80	16	2.9	15.5	11	22	9.9	21.8	(9.2, 11.0)	(20.9, 23.1)
LIP	F	84	76	15.7	2.3	15.5	10	21	10.9	20.1	(10.2, 11.7)	(19.3, 21.1)
INS	M	11	8	14.5	2	14.9	10.8	17.1	NA	NA	(NA, NA)	(NA, NA)
INS	F	17	14	12.3	3.1	11.1	9	16.8	NA	NA	(NA, NA)	(NA, NA)
MG	M	45	44	2	0.13	2	1.8	2.2	1.73	2.27	(1.68, 1.78)	(2.21, 2.32)
MG	F	46	43	1.99	0.11	2	1.8	2.2	1.76	2.21	(1.72, 1.81)	(2.17, 2.25)
TSH	M	82	80	0.6	0.3	0.6	0.1	1.2	0	1.2	BFA	(1.1, 1.3)
TSH	F	79	76	0.78	0.43	0.67	0.1	1.77	BFA	1.59	BFA	(1.42, 1.80)
T3	M	82	78	221	33	222	144	304	156	285	(146, 167)	(274, 295)
T3	F	79	72	213	33	216	122	297	148	278	(138, 159)	(267, 289)
T4	M	82	81	4	1.1	3.7	2.1	6.6	1.6	6.2	(1.1, 1.8)	(5.8, 6.6)
T4	F	79	77	4.2	1.1	4	2.2	6.9	1.8	6.4	(1.5, 2.2)	(6.0, 6.8)
CRPHS	M	81	79	1.3	0.66	1.3	0.2	2.8	BFA	2.61	BFA	(2.42, 2.82)
CRPHS	F	46	42	1.24	0.62	1.2	0.2	2.6	0.03	2.46	BFA	(2.19, 2.72)

Note: See Table 1 for abbreviations of individual analytes.

Abbreviations: BFA, beyond the feasibility of analysis; CI, confidence interval; F, female; LRI, lower reference limit; M, male; N, animal number/sample size; RI, reference interval; SD, standard deviation; URI, upper reference limit.

4 | DISCUSSION

Cynomolgus monkeys are often the most pharmacologically and metabolically relevant animal species for nonclinical safety assessment, especially for biologics.[24–26] Target organ development and age correlations between the monkey and the intended patient population are critical factors for study design. The juvenile toxicity study is typically conducted in postweaning monkeys starting at 10 to 12 months of age, whereas safety assessments of biologics require using monkeys of sexual maturity. For general toxicity studies, the starting ages of monkeys vary from 2 to 5 years. In the current study, therefore, we reviewed the age- or sex-related differences in body weights and hematologic, coagulation, and serum biochemical analyte values and saw sexual dimorphism in body weights at all ages from 2 to 10 years. Sex-related changes in mean hematologic and serum biochemical analytes also occurred. Age-related changes in mean hematologic and serum biochemical analytes were also seen. The only difference in clinical pathology analytes unique to the 2 to <3 years of age group were age-related lower globulin concentrations compared with older animals. No age- or sex-related differences were seen with the coagulation analytes. Hematologic, coagulation, and serum biochemical RIs and body weights have been previously reported for cynomolgus monkeys with a small number of animals, limited age ranges, mixed genders, and/or different geographic origins.[16,17] In the current study, we report similar indices in a large cohort of cynomolgus monkeys of Mauritian origin, which will provide useful RIs worldwide, especially for laboratories using similar testing methods, animal age ranges, and animal origins.

The age- and sex-related changes in serum biochemical analyte values are related to physiology or organ system development.[18,19] Age-related decreases in ALP activity and phosphorus concentrations reflect decreased bone formation in older animals, and higher ALP and GGT activities in male than female monkeys have also been previously reported in the literature.[18,27] Sex differences in ALP activity have been reported in a similar species, the Japanese macaque, which has higher ALP activities in males likely associated with growth in males; during which time females have stopped growing. It could also be associated with the expression of secondary sex characteristics induced by sex hormones.[28] Similarly, higher GGT activity has been reported in human males than females, which is also thought to be due to sex hormones.[29] Age-related increases in creatinine concentrations and higher creatinine levels in male than female monkeys are likely due to increased muscle mass with age and in males, respectively.[27] There was a trend for higher serum lipids in older female monkeys compared with younger female monkeys and similarly-aged male monkeys, which was due to higher triglyceride concentrations. Cholesterol was also higher in older female monkeys compared to similarly-aged male monkeys. It was recently published that, as in humans, female cynomolgus monkeys tend to have higher serum lipids than males.[30] Sex-specific differences in lipid and glucose metabolism are known to occur in both humans and nonhuman primates and may be due at least in part to the unique requirements of females for gestation and/or lactation.[31] The slightly lower globulin concentrations in male and female monkeys 2 to <3 years of age compared with older monkeys is consistent with other reports showing increasing globulin concentrations with age, which could be due, at least in part, to increasing environmental antigen exposure and adaptive immunity.[27]

The age- and sex-related changes in hematologic analytes seem to be mostly related to physiology and/or environmental exposure.[10,16–17] Lower lymphocyte counts in older monkeys of both sexes are consistent with the literature.[32] RETIC counts increased with age in both sexes and were higher in older female monkeys compared to similarly aged male monkeys. While we did not find anything in the literature regarding age- or sex-related differences in RETIC values, sex-related differences in RETIC values have been seen in our internal historical RIs where females had a higher upper RI than males. In this study, despite the increased RETIC values, no significant differences in RBC mass measurands (RBC, hemoglobin [HGB], and hematocrit [HCT]) were observed. Increased RETIC values without concurrent decreases in the RBC mass measurands can indicate that the bone marrow is responding to a need for increased RBC production. Because RETICs only circulate for a few days and RBCs circulate for significantly longer (~100 days in cynomolgus monkey), a significant lag in decreased RBC, HGB, and HCT values could occur compared with increased RETIC counts.[33] In this study, higher RETIC counts in older females may be related to menstruation-related blood loss which was also suspected to be the cause of lower RBC measurands in older females compared to similarly-aged males in a large cohort of Asian cynomolgus monkeys.[27]

The hematologic, coagulation, and serum biochemical intervals for cynomolgus monkeys are variable in the literature.[27,32,34] The geographic origin might have impacted the hematologic and clinical biochemical analytes.[9,19,35] It has been reported that Mauritian monkeys have higher RBC counts but lower RETIC and WBC counts, and MCV and MCH values than Asian monkeys.[9] Mauritian monkeys have higher serum calcium and lower serum phosphorus than Asian monkeys.[9] Cynomolgus monkeys indigenous to the Philippines have lower creatine phosphokinase and alanine aminotransferase values than the Mauritian or Vietnamese monkeys,[9] and Vietnamese monkeys had lower ALP and aspartate aminotransferase than Philippine and Mauritian monkeys.[9] Among Mauritian monkeys, many hematologic and biochemical analytes measurements differ between purpose-bred and captured animals.[19]

In cynomolgus monkeys, sexual dimorphism in body sizes or weights has been reported to become significant after 3 to 4 years of age.[37] In a large cohort of Asian cynomolgus monkeys (588 males and 1930 females), there was no sex-related difference in body weights before 4 years of age.[17] In males, body weights increased dramatically after 4 to 5 years, peaked at 14 to 15 years (~8.40 kg), and declined after 17 years of age. In females, body weights increased gradually after birth, peaked at 12 to 13 (~5.0 kg) years, and declined after 15 years of age.[17] In the current study, body weights were significantly higher in males than

females of all age groups from 2 to 10 years of age, suggesting the sexual dimorphism in body sizes as early as at least 2 years of age in Mauritian cynomolgus monkeys. It has been reported that the cynomolgus monkey of Mauritian origin is generally larger in body weight/size and becomes sexually mature 1 to 2 years earlier than Asia cynomolgus monkeys.[9,38] In the current study, body weights of Mauritian monkeys peaked at 7 to 8 years of age in both males (7.9 kg) and females (5.5 kg). Apparently, body weight reaches its peak in Mauritian monkeys (7 to 8 years of age) earlier than in Asian monkeys (12 to 15 years of age). Once the plateau is reached, body weights are comparable between Mauritian and Asian cynomolgus monkeys. Age and body weight have been proposed as a predictor of puberty and clinical pathology analyte values in cynomolgus monkeys.[38–42] Correlations between body weight and clinical pathology analytes have been observed in female cynomolgus monkeys.[42] Body weight has been shown to correlate positively with HGB, HCT, MCV, glucose, triglycerides, leptin, and insulin levels.[42] In our study, triglyceride levels were higher in older females as compared to younger females and in females as compared to similarly-aged males. Body weights alone are not a reliable predictor of clinical pathology analyte values in cynomolgus monkeys.

Clinical pathology RIs play important roles in clinical laboratory diagnoses and nonclinical safety assessments, especially in large animal studies where animal numbers are often limited and for those labs where appropriate internal references have not been established. Guidelines on determining, establishing, and verifying controls or RIs have been established for both clinical and veterinary laboratories.[14,36,43] However, many other factors can influence the results and interpretation of both internal and published clinical pathology RIs, such as variations associated with individual animals, laboratory settings, study-related procedures, and environmental conditions.[23,27,35,44,45] Animal factors might include animal species, origin, numbers, sex, age, health status, inter-, and intra-animal variability, and animal husbandry and care practices. The laboratory or facility variations can include species- or parameter-specific assay methods, instruments and reagents, sample frequency and preparations, and technologic variation. The study-related procedures include study design variables, such as handling frequency and intensity, dosing methods and devices, sample collection frequency, volume, invasiveness, fasting states, anesthesia restraints, instrumentation, such as telemetry or catheterization, and environmental stress. Thus, it is prudent to adopt a weight of evidence approaches to use and interpret RI ranges or values, especially when using external reference datasets.

There were some limitations in the current study. The animals were restricted to cynomolgus monkey of Mauritian origin only so caution should be taken when using the RIs for cynomolgus monkey of other origins. Most animals included in this data set were 3 to 5 years of age and while at these ages both sexes were generally equally represented there were lesser numbers of females than males in the 2 to <3 years of age group. So RIs provided for the 3 to <4 years of age group were more robust than the RIs for the 2 to <3 years of age group and the RI for males 2 to <3 years of age were more robust than the RI for similarly-aged females. This dataset was generated using Pfizer animal use and care conditions, analytic instruments, and analytical methods so there may be variations from other animal care facilities and laboratory settings.

In summary, we saw sexual dimorphism for body weights from 2 to 10 years of age in cynomolgus monkeys of Mauritian origin. Sex-related differences were noted in RETIC counts, creatinine, cholesterol, and triglyceride concentrations, and ALP and GGT activities. Age-related differences were noted in RETIC and lymphocyte counts, creatinine, triglyceride, phosphorus and globulin concentrations, and ALP and GGT activities. The youngest (2 to <3 year) age group had the fewest number of clinical pathologic analyte differences including ALP and GGT activity differences which occurred in all age groups from 2 to 10 years and age-related lower globulin concentrations.

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DISCLOSURE

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