Data Article

Toxicological data of rats and rabbits: Sub-chronic testing of recombinant HPV vaccine through oral and intranasal routes

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A B S T R A C T

Current article illustrates the data of body weight, biochemical, haematological profile, and organ weights of rats and rabbits administered with recombinant human papilloma virus (HPV) vaccine, along with genotoxicity effect. The data was collected from nonclinical safety/toxicity and immune response evaluations of recombinant Salmonella typhi expressing the HPV 16 and 18 L1 proteins as vaccine. The intended clinical route of vaccine administration is through oral route, whereas it is established fact that attenuated S. typhi could not colonize in laboratory animals. In view of this it is challenging to undertake the nonclinical safety/toxicity evaluations following the regulatory guidelines. Hence sub chronic safety/toxicity testing was carried out in rat and rabbits by administration of HPV vaccine through oral (intended clinical route) and innovative intranasal routes. The prophylactic dose derived from adult human clinical dose (2 × 10⁹CFU/70 kg) was administered to SD rats (PD: 0.18 × 10⁹CFU/kg) and New Zealand White (NZW) rabbits.

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Subject data
Specific parameters
Type
How

format data of subject were for of Y. Srinivasa data acquired area different in levels response assessing genotoxicity veil plexus of (25% tion through ministered through rats (PD: 0.9 × 10^9 CFU/kg) and rabbits (AD: 0.45 × 10^9 CFU/kg) through intranasal route only. The repeated doses were administered on 3rd and 5th days of post-exposure of 1st dose through specified routes and test compound effects in relation with time of exposure was assessed by euthanizing animals and data collection at different time points i.e. 15th (25% of animals), 29th (25% of animals) and 93rd days (50% of animals) of post-exposure of 1st dose. The retro-orbital plexus blood was collected before euthanizing animals to unveil the biochemical and haematological profile. The data on genotoxicity effect of test compound, if any, was obtained by assessing the bone-marrow micronucleus assay. The immune response and allergenicity in terms of specific IgG and IgE levels against HPV 16 and 18 L1 proteins were determined in mice. The raw data of various parameters collected at different time points were compiled and computed according to the groups. The haematological profile and organ weights data can be used as reference data for SD rats and NZW rabbits for future studies.

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Specifications Table

| Subject | Pharmacology, Toxicology and Pharmaceuticals Science |
|---------|------------------------------------------------------|
| Specific subject area | Sub chronic Toxicity Testing of HPV 16 & 18 L1 Expressing S. typhi |
| Type of data | Tables |
| How data were acquired | Rats and rabbits were administered with prophylactic dose (PD) and average dose (5xPD) of recombinant S. typhi expressing HPV 16 & 18 L1 proteins through oral and intranasal routes. Repeated exposure effect of test compound was assessed by administration of HPV vaccine on 3rd and 5th day through the specified routes. Test compound effects on route and dose of administration was assessed in blood and recording vital organ weights after euthanizing animals at different time points. |
| data format | analysed data of mean and sd |
| Parameters for data collection | Haematological profile was collected using automated blood cell counter as per the manufacturer’s instructions and guidelines (Serono Baker System 9120 CP+, USA). The organ weights were recorded on weighing balance (Sartorius, SECURA125–1OBR). Data was compiled and computed to derive mean and standard deviation (SD) using SPSS 15.0 windows version. |
| Description of data collection | Blood was collected from retro-orbital plexus using microhematocrit capillaries (Fisher Scientific # 22–362,566) into K2EDTA tubes (BD Vacutainer). Haematological investigations includes total white blood cell (WBC) count, red blood cell (RBC) count, haemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelet count, mean platelet volume (MPV) and differential leukocytes counts. The data collected from all the animals of each and every group was compiled and computed. |

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Value of the Data

• The data of current report is extremely useful as it obtained from rats and rabbits administered with attenuated S. typhi Ty21a expressing HPV 16 & 18 L1 Protein as vaccine candidate.
• Further, the haematological profile data is useful as it was collected from laboratory animals exposed to HPV Vaccine through intended clinical oral and innovative intranasal routes.
• The data of vital organ weights of rats and rabbits is used as reference data.
• This data helps the pharmacologists, regulatory agencies and policy makers to consider the alternate and innovative methods of ‘New Drug Testing’ procedures.

1. Data Description

The data of current article describes about various parameters analysed as body weights, biochemical, haematological profile in blood samples and organ weights along with genotoxicity effect, collected from rats and rabbits administered the recombinant S. typhi TY21a HPV (rSt.HPV) expressing HPV 16 and 18 L1 proteins as vaccine through oral and intranasal routes. Blood was collected before euthanizing at different time points (post-exposure of 1st dose) after three successive dosing of HPV vaccine, at the same time points vital organs were collected and recorded the weights after euthanizing the animals. The raw data from all the animals of different groups were compiled and computed accordingly.

Data of Table 1 comprises of body weights of rats used for sub-chronic toxicity study testing of the rSt.HPV expressing 16 and 18 L1 proteins.

Data of Table 2 comprised of body weights of rabbits used to test the sub-chronic toxicity of rSt.HPV expressing 16 and 18 L1 proteins.

Data of Tables 3.1–3.3 consists of haematological profile of rats euthanized on 15th, 29th and 93rd day of post-exposure of 1st dose administration of HPV vaccine as part of sub-chronic testing. The haematological profile includes haemoglobin, red blood cells (RBC), white blood cells (WBC), haematocrit (HCT), mean corpuscular volume (MCV), and mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelets, neutrophils, lymphocytes, monocytes, eosinophils from rats.

Similarly, the haematological profile of rabbits euthanized on 15th, 29th and 93rd days of post-administration of 1st dose of recombinant HPV vaccine were given in Tables 4.1–4.3, respectively.

Data of Table 5 comprised of biochemical profile of rats used for subchronic testing of rSt.HPV expressing HPV 16 and 18 L1 proteins. The biochemical profile includes ALT, AST, ALP, creatinine, total bilirubin, urea, glucose, calcium, total protein and albumin levels. Similarly, the Table 6 composed of biochemical profile of rabbits administered with rSt.HPV expressing HPV 16 and 18 L1 proteins as part of subchronic testing.

The data on weights of vital organs viz. brain, heart, kidneys, liver, lung, spleen and testis of rats euthanized on 15th, 29th and 93rd days were given in Tables 7.1–7.3.

Similarly, the data on weights of vital organs of rabbits administered with HPV vaccine euthanized on 15th day, 29th day and 93rd day were given in Tables 8.1–8.3.
Table 1

| Sex                | Baseline | 8th Day | 16th Day | 22nd Day | 29th Day | 43rd Day | 57th Day | 71st Day | 89th Day |
|--------------------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| Vehicle Control (VC)  |          |         |          |          |          |          |          |          |          |
| ♂                  | 182.10   | 208.00  |          |          |          |          |          |          |          |
|                    | 216.60   | 234.60  |          |          |          |          |          |          |          |
|                    | 218.30   | 235.50  |          |          |          |          |          |          |          |
|                    | 191.50   | 210.00  | 237.20   | 240.30   |          |          |          |          |          |
|                    | 238.60   | 258.30  | 264.50   | 278.70   |          |          |          |          |          |
|                    | 224.20   | 247.70  | 269.30   | 277.50   |          |          |          |          |          |
|                    | 202.70   | 238.00  | 262.60   | 267.50   | 314.40   | 362.20   | 391.50   | 405.40   | 419.00   |
|                    | 196.80   | 189.00  | 223.90   | 235.20   | 266.50   | 308.90   | 329.60   | 342.10   | 367.00   |
|                    | 213.60   | 225.60  | 255.30   | 257.60   | 284.50   | 317.50   | 333.90   | 346.70   | 336.00   |
|                    | 207.90   | 211.20  | 209.80   | 208.60   | 241.30   | 282.70   | 310.30   | 319.30   | 335.00   |
|                    | 231.30   | 243.10  | 237.90   | 236.70   | 275.20   | 306.90   | 352.70   | 373.20   | 381.00   |
|                    | 239.20   | 231.50  | 236.50   | 240.30   | 261.60   | 322.80   | 338.60   | 350.90   | 360.00   |
| ▪                  | 199.20   | 208.30  |          |          |          |          |          |          |          |
|                    | 212.40   | 207.40  |          |          |          |          |          |          |          |
|                    | 199.20   | 210.60  |          |          |          |          |          |          |          |
|                    | 182.50   | 199.90  | 217.40   | 195.50   |          |          |          |          |          |
|                    | 196.70   | 215.30  | 210.50   | 197.70   |          |          |          |          |          |
|                    | 193.70   | 179.80  | 184.80   | 169.20   |          |          |          |          |          |
|                    | 191.90   | 207.30  | 206.90   | 192.30   | 216.20   | 215.60   | 223.80   | 233.20   | 224.00   |
|                    | 200.10   | 218.80  | 209.60   | 188.70   | 229.60   | 236.90   | 242.60   | 256.50   | 251.00   |
|                    | 197.10   | 203.30  | 196.80   | 205.80   | 213.50   | 227.50   | 237.50   | 248.30   | 252.00   |
|                    | 192.90   | 226.00  | 237.40   | 215.80   | 235.50   | 236.30   | 255.40   | 275.10   | 250.00   |
|                    | 191.00   | 200.60  | 203.90   | 171.80   | 196.60   | 215.90   | 244.30   | 259.20   | 253.00   |
|                    | 208.10   | 228.50  | 236.30   | 207.60   | 238.50   | 243.50   | 261.50   | 291.90   | 268.00   |

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Table 1 (continued)

| Sex          | Baseline | 8th Day | 16th Day | 22nd Day | 29th Day | 43rd Day | 57th Day | 71st Day | 89th Day |
|--------------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| ♂            | 208.60   | 223.50  | Euthanized on 15th Day |
|              | 217.20   | 255.40  |          |          |          |          |          |          |          |
|              | 225.10   | 244.70  |          |          |          |          |          |          |          |
|              | 175.90   | 196.80  | 206.40   | 210.30   |          |          |          |          |          |
|              | 216.40   | 208.40  | 237.60   | 239.60   |          |          |          |          |          |
|              | 189.90   | 215.30  | 243.80   | 237.70   |          |          |          |          |          |
|              | 200.70   | 232.50  | 265.70   | 256.80   | 294.60   | 332.10   | 348.30   | 358.70   | 354.00   |
|              | 217.10   | 249.60  | 277.40   | 258.90   | 276.30   | 287.60   | 347.50   | 359.90   | 387.00   |
|              | 199.40   | 209.80  | 237.20   | 250.60   | 278.60   | 288.70   | 334.40   | 348.20   | 352.00   |
|              | 229.60   | 232.60  | 237.80   | 229.80   | 268.50   | 320.80   | 354.20   | 366.20   | 371.00   |
|              | 232.30   | 250.70  | 251.40   | 242.50   | 273.60   | 313.70   | 351.30   | 361.20   | 378.00   |
|              | 276.40   | 285.60  | 273.20   | 263.40   | 299.90   | 356.40   | 392.10   | 406.90   | 410.00   |
| ♂            | 250.10   | 204.60  | Euthanized on 15th Day |
|              | 183.30   | 191.30  |          |          |          |          |          |          |          |
|              | 189.70   | 201.60  | 208.90   | 209.60   |          |          |          |          |          |
|              | 187.60   | 187.80  | 200.80   | 202.20   |          |          |          |          |          |
|              | 201.00   | 216.60  | 234.40   | 240.70   |          |          |          |          |          |
|              | 199.40   | 211.30  | 201.40   | 210.90   | 227.00   | 239.10   | 245.20   | 255.30   | 253.00   |
|              | 203.20   | 223.40  | 213.40   | 213.60   | 233.80   | 246.80   | 248.30   | 262.10   | 248.00   |
| ♀            | 205.10   | 204.60  |          |          |          |          |          |          |          |
|              | 183.30   | 192.00  |          |          |          |          |          |          |          |
|              | 189.70   | 201.60  | 208.90   | 209.60   |          |          |          |          |          |
|              | 187.60   | 187.80  | 200.80   | 202.20   |          |          |          |          |          |
|              | 201.00   | 216.60  | 234.40   | 240.70   |          |          |          |          |          |
|              | 199.40   | 211.30  | 201.40   | 210.90   | 227.00   | 239.10   | 245.20   | 255.30   | 253.00   |
|              | 203.20   | 223.40  | 213.40   | 213.60   | 233.80   | 246.80   | 248.30   | 262.10   | 248.00   |
|              | 199.90   | 203.50  | 196.30   | 204.50   | 231.80   | 233.40   | 250.50   | 258.90   | 256.00   |
|              | 201.50   | 190.30  | 207.50   | 214.60   | 217.50   | 226.10   | 233.40   | 243.20   | 230.00   |
|              | 203.40   | 206.30  | 231.50   | 236.10   | 241.30   | 253.40   | 262.40   | 272.60   | 275.00   |

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Table 1 (continued)

| Sex       | Baseline | 8th Day | 16th Day | 22nd Day | 29th Day | 43rd Day | 57th Day | 71st Day | 89th Day |
|-----------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| ♂         | 212.30   | 248.60  |          |          |          |          |          |          |          |
|           | 202.80   | 216.60  |          |          |          |          |          |          |          |
|           | 205.10   | 231.30  |          |          |          |          |          |          |          |
|           | 203.30   | 216.70  |          |          |          |          |          |          |          |
|           | 204.10   | 188.70  |          |          |          |          |          |          |          |
|           | 249.40   | 276.60  |          |          |          |          |          |          |          |
|           | 191.10   | 222.60  | 256.40   | 238.80   | 290.20   | 334.70   | 363.20   | 372.80   | 396.00   |
|           | 209.70   | 244.20  | 260.40   | 245.50   | 280.30   | 336.50   | 362.10   | 374.70   | 383.00   |
|           | 255.50   | 273.60  | 290.30   | 287.60   | 322.90   | 358.90   | 385.70   | 400.00   | 417.00   |
|           | 210.10   | 212.50  | 222.80   | 219.50   | 240.50   | 287.30   | 322.30   | 345.20   | 364.00   |
|           | 254.10   | 279.00  | 286.30   | 265.40   | 303.50   | 351.70   | 382.70   | 401.20   | 411.00   |
|           | 238.50   | 261.30  | 282.90   | 267.30   | 307.90   | 364.20   | 396.30   | 408.90   | 419.00   |
| ♂         | 200.80   | 226.60  |          |          |          |          |          |          |          |
|           | 236.80   | 240.40  |          |          |          |          |          |          |          |
|           | 205.20   | 222.10  |          |          |          |          |          |          |          |
|           | 190.20   | 199.80  |          |          |          |          |          |          |          |
|           | 183.50   | 199.50  | 199.80   | 195.30   |          |          |          |          |          |
|           | 208.90   | 221.90  | 233.00   | 232.40   |          |          |          |          |          |
|           | 183.50   | 200.10  | 203.70   | 199.90   | 216.20   | 228.70   | 230.80   | 254.70   | 244.00   |
|           | 199.70   | 197.40  | 225.20   | 209.60   | 229.30   | 234.60   | 243.10   | 270.10   | 265.00   |
|           | 189.80   | 185.70  | 207.90   | 196.40   | 220.80   | 235.80   | 233.20   | 253.20   | 245.00   |
|           | 198.60   | 196.60  | 216.70   | 200.70   | 221.20   | 227.70   | 234.10   | 255.50   | 246.00   |
|           | 218.40   | 238.20  | 260.90   | 273.30   | 254.60   | 253.40   | 263.90   | 283.90   | 278.00   |
|           | 205.60   | 215.70  | 229.70   | 225.60   | 230.00   | 233.20   | 238.50   | 251.40   | 256.00   |

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| Sex | Baseline | 8th Day | 16th Day | 22nd Day | 29th Day | 43rd Day | 57th Day | 71st Day | 89th Day |
|-----|----------|---------|----------|----------|----------|----------|----------|----------|---------|
| ♂   | 207.30   | 216.90  |          |          |          |          |          |          |         |
|     | 204.80   | 226.10  |          |          |          |          |          |          |         |
|     | 222.10   | 236.50  |          |          |          |          |          |          |         |
|     | 193.30   | 199.60  | 207.50   | 213.20   |          |          |          |          |         |
|     | 253.60   | 278.40  | 296.50   | 305.20   |          |          |          |          |         |
|     | 268.70   | 295.30  | 320.90   | 326.70   |          |          |          |          |         |
|     | 186.40   | 190.80  | 195.60   | 197.20   | 241.90   | 305.30   | 330.30   | 358.20   | 380.00  |
|     | 229.00   | 257.80  | 262.90   | 260.40   | 296.60   | 335.20   | 373.20   | 391.30   | 400.00  |
|     | 201.40   | 215.80  | 244.40   | 247.40   | 279.50   | 305.80   | 339.40   | 354.20   | 368.00  |
|     | 230.50   | 249.60  | 264.80   | 264.90   | 291.20   | 314.20   | 340.50   | 354.50   | 363.00  |
|     | 209.50   | 228.40  | 261.60   | 278.10   | 310.50   | 349.20   | 369.10   | 385.80   | 402.00  |
|     | 229.80   | 247.60  | 264.40   | 275.50   | 303.70   | 334.50   | 362.30   | 365.70   | 376.00  |
| ♀   | 195.30   | 198.70  |          |          |          |          |          |          |         |
|     | 186.90   | 188.80  |          |          |          |          |          |          |         |
|     | 215.30   | 226.60  |          |          |          |          |          |          |         |
|     | 186.10   | 198.30  | 215.50   | 224.80   |          |          |          |          |         |
|     | 192.70   | 203.50  | 213.60   | 223.40   |          |          |          |          |         |
|     | 200.70   | 209.60  | 224.10   | 224.20   |          |          |          |          |         |
|     | 192.50   | 210.00  | 226.10   | 234.20   | 235.30   | 246.20   | 278.50   | 275.70   | 274.00  |
|     | 195.40   | 215.30  | 224.10   | 230.50   | 238.70   | 241.40   | 241.90   | 262.30   | 258.00  |
|     | 180.40   | 196.60  | 216.40   | 230.20   | 232.30   | 255.80   | 264.30   | 275.80   | 271.00  |
|     | 222.10   | 223.00  | 226.20   | 221.20   | 239.80   | 241.90   | 254.70   | 271.00   | 262.00  |

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Table 1 (continued)

|       | Sex | Baseline | 8th Day | 16th Day | 22nd Day | 29th Day | 43rd Day | 57th Day | 71st Day | 89th Day |
|-------|-----|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| ♂     |     |          |         |          |          |          |          |          |          |          |
| Prophylactic Dose – Oral (PD-OR) |     |          |         |          |          |          |          |          |          |          |
|       |     | 183.80   | 225.80  |          |          |          |          |          |          |          |
|       | 217.60 | 255.30   |         |          |          |          |          |          |          |          |
|       | 254.70 | 256.80   |         |          |          |          |          |          |          |          |
|       | 206.90 | 229.20   |         |          |          |          |          |          |          |          |
|       | 195.70 | 215.90   | 219.80  | 229.50   |          |          |          |          |          |          |
|       | 202.30 | 231.30   | 264.60  | 263.90   |          |          |          |          |          |          |
|       | 170.60 | 202.50   | 230.70  | 246.70   | 266.40   | 304.80   | 329.80   | 343.80   | 355.00   |          |
|       | 262.90 | 296.50   | 303.80  | 321.20   | 370.50   | 417.70   | 448.30   | 455.70   | 471.00   |          |
|       | 217.90 | 235.60   | 227.60  | 230.40   | 265.50   | 302.30   | 332.80   | 338.90   | 344.00   |          |
|       | 186.20 | 219.50   | 236.10  | 233.40   | 246.30   | 270.80   | 291.50   | 292.30   | 297.00   |          |
|       | 228.70 | 235.60   | 244.80  | 247.20   | 268.20   | 275.60   | 298.80   | 306.30   | 321.00   |          |
|       | 236.80 | 243.70   | 259.00  | 266.10   | 293.20   | 329.80   | 363.20   | 373.50   | 396.00   |          |
| ♂     |     |          |         |          |          |          |          |          |          |          |
|       | 189.60 | 200.10   |         |          |          |          |          |          |          |          |
|       | 210.70 | 234.30   |         |          |          |          |          |          |          |          |
|       | 222.80 | 224.80   |         |          |          |          |          |          |          |          |
|       | 174.80 | 207.30   | 203.80  | 203.50   |          |          |          |          |          |          |
| ♂     |     |          |         |          |          |          |          |          |          |          |
|       | 209.40 | 215.40   | 220.30  | 208.50   |          |          |          |          |          |          |
|       | 231.60 | 215.50   | 223.20  | 227.70   |          |          |          |          |          |          |
|       | 214.20 | 217.80   | 224.20  | 233.20   | 234.90   | 228.30   | 235.60   | 249.20   | 241.00   |          |
|       | 197.80 | 215.30   | 211.70  | 206.60   | 231.40   | 238.90   | 242.40   | 265.30   | 255.00   |          |
|       | 201.70 | 209.80   | 200.30  | 190.50   | 221.60   | 226.70   | 233.60   | 249.00   | 249.00   |          |
| ♂     |     |          |         |          |          |          |          |          |          |          |
|       | 212.60 | 225.70   | 221.80  | 210.90   | 239.90   | 251.90   | 254.70   | 271.30   | 288.00   |          |
|       | 207.40 | 216.00   | 218.90  | 208.50   | 224.50   | 236.20   | 240.40   | 253.70   | 259.00   |          |
| ♂     |     |          |         |          |          |          |          |          |          |          |
|       | 216.80 | 220.10   | 230.90  | 228.80   | 241.60   | 245.10   | 246.50   | 262.80   | 252.00   |          |

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| Sex            | Baseline | 8th Day | 16th Day | 22nd Day | 29th Day | 43rd Day | 57th Day | 71st Day | 89th Day |
|----------------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| Average Dose – Intra-Nasal (AD-IN) |          |         |          |          |          |          |          |          |          |
| ♂             | 201.40   | 197.30  |          |          | 227.50   | 288.80   |          |          |          |
| 201.00        | 248.70   |         |          |          | 292.60   | 317.40   | 339.40   | 343.10   | 333.00   |
| 286.10        | 298.90   |         |          |          | 347.60   | 351.20   | 364.00   |          |          |
| 226.20        | 255.50   | 283.20  | 278.80   |          |          |          |          |          |          |
| 201.00        | 226.80   | 246.50  | 238.80   |          |          |          |          |          |          |
| 221.40        | 223.50   | 251.70  | 263.40   |          |          |          |          |          |          |
| 212.30        | 226.80   | 247.80  | 241.50   | 277.50   | 317.40   | 339.40   | 343.10   | 333.00   |          |
| 221.00        | 239.30   | 244.20  | 242.60   | 292.60   | 364.30   | 403.80   | 435.20   | 461.00   |          |
| 198.60        | 228.80   | 250.50  | 264.10   | 277.80   | 316.20   | 347.60   | 351.20   | 364.00   |          |
| 208.60        | 244.30   | 270.10  | 259.50   | 313.20   | 321.60   | 389.20   | 405.30   | 412.00   |          |
| 214.40        | 230.60   | 245.20  | 236.80   | 278.20   | 360.10   | 347.80   | 359.70   | 360.00   |          |
| 236.10        | 240.00   | 271.00  | 283.10   | 298.30   | 321.20   | 345.90   | 364.30   | 375.00   |          |
| ♀             | 203.20   | 216.30  |          |          |          |          |          |          |          |
| 203.20        | 216.30   |         |          |          |          |          |          |          |          |
| 201.40        | 197.30   |         |          |          | 227.50   | 288.80   |          |          |          |
| 201.00        | 248.70   |         |          |          | 292.60   | 317.40   | 339.40   | 343.10   | 333.00   |
| 286.10        | 298.90   |         |          |          | 347.60   | 351.20   | 364.00   |          |          |
| 226.20        | 255.50   | 283.20  | 278.80   |          |          |          |          |          |          |
| 201.00        | 226.80   | 246.50  | 238.80   |          |          |          |          |          |          |
| 221.40        | 223.50   | 251.70  | 263.40   |          |          |          |          |          |          |
| 212.30        | 226.80   | 247.80  | 241.50   | 277.50   | 317.40   | 339.40   | 343.10   | 333.00   |          |
| 221.00        | 239.30   | 244.20  | 242.60   | 292.60   | 364.30   | 403.80   | 435.20   | 461.00   |          |
| 198.60        | 228.80   | 250.50  | 264.10   | 277.80   | 316.20   | 347.60   | 351.20   | 364.00   |          |
| 208.60        | 244.30   | 270.10  | 259.50   | 313.20   | 321.60   | 389.20   | 405.30   | 412.00   |          |
| 214.40        | 230.60   | 245.20  | 236.80   | 278.20   | 360.10   | 347.80   | 359.70   | 360.00   |          |
| 236.10        | 240.00   | 271.00  | 283.10   | 298.30   | 321.20   | 345.90   | 364.30   | 375.00   |          |

Table 1 (continued)
| Sex         | Baseline | 8th Day | 19th Day | 26nd Day | 37th Day | 50th Day | 64th Day | 78th Day | 89th Day |
|-------------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| Vehicle Control (VC) ♂️ | 1520.0   | 1714.0  | Euthanized on 15th Day |
| 1870.0      | 1979.0   |         |          |          |          |          |          |          |
| 1970.0      | 2008.0   |         |          |          |          |          |          |          |
| 1502.0      | 1577.0   | 1560.0  | 1502.0   | Euthanized on 29th Day |
| 2238.0      | 2417.0   | 2630.0  | 2741.0   |          |          |          |          |          |
| 1621.0      | 1690.0   | 1740.0  | 1670.0   | 1773.0   | 1793.0   | 1787.0   | 1784.0   | 1797.5   |
| 1675.0      | 1778.0   | 1869.0  | 1866.0   | 1835.0   | 1900.0   | 1937.0   | 1962.0   | 1956.2   |
| 1970.0      | 2174.0   | 2219.0  | 2195.1   | 2214.0   | 2271.0   | 2349.0   | 2360.0   | 2292.0   |
| 2040.0      | 2353.0   | 2544.0  | 2723.0   | 2706.0   | 2762.0   | 2878.0   | 2823.0   | 2555.0   |
| 2261.0      | 2475.0   | 2537.0  | 2508.0   | 2618.0   | 2663.0   | 2443.0   | 2430.0   | 2440.6   |
| 1884.0      | 1888.0   |         | Euthanized on 15th Day |
| 2399.0      | 2486.2   |         |          |          |          |          |          |          |
| 1778.0      | 2033.4   | 2102.5  | 2305.5   | Euthanized on 29th Day |
| 1768.0      | 1881.8   | 1939.3  | 2046.6   |          |          |          |          |          |
| 2100.0      | 2223.4   | 2426.0  | 2473.1   |          |          |          |          |          |
| 1917.0      | 1999.4   | 2333.0  | 2354.0   | 2365.4   | 2481.0   | 2530.0   | 2597.0   | 2616.4   |
| 2086.0      | 2194.3   | 2553.0  | 2682.7   | 2579.0   | 2599.0   | 2690.0   | 2740.0   | 2539.0   |
| 2184.0      | 2333.2   | 2673.0  | 2723.3   | 2722.0   | 2745.0   | 2869.0   | 2881.0   | 2848.7   |
| 1967.0      | 2095.4   | 2226.0  | 2344.3   | 2340.0   | 2406.0   | 2497.0   | 2477.0   | 2544.0   |
| 2168.0      | 2335.6   | 2521.0  | 2532.7   | 2525.0   | 2562.0   | 2709.0   | 2702.0   | 2674.5   |

(continued on next page)
| Sex             | Baseline | 8th Day | 19th Day | 26nd Day | 37th Day | 50th Day | 64th Day | 78th Day | 89th Day |
|-----------------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| Experimental Control | 1320.0   | 1466.0  | Euthanized on 15th Day |
| Intra-Nasal (EC-IN)  | 1581.0   | 1269.0  | Euthanized on 29th Day |
|                 | 2260.0   | 2429.0  |          |          |          |          |          |          |          |
|                 | 2125.0   | 2322.0  | 2513.0   | 2630.0   | Euthanized on 29th Day |
|                 | 1826.0   | 1883.0  | 2057.0   | 2085.0   |          |          |          |          |          |
|                 | 2051.0   | 2185.0  | 2255.0   | 2353.0   | 2440.0   | 2360.0   | 2510.0   | 2454.0   | 2474.2   |
|                 | 1970.0   | 2158.0  | 2400.0   | 2448.0   | 2501.0   | 2470.0   | 2437.0   | 2460.0   | 2518.0   |
|                 | 2066.0   | 2226.0  | 2369.0   | 2414.0   | 2439.0   | 2486.0   | 2528.0   | 2487.0   | 2540.0   |
|                 | 2208.0   | 2381.0  | 2690.0   | 2812.0   | 2802.0   | 2815.0   | 2893.0   | 2905.0   | 2954.0   |
|                 | 2232.0   | 2353.0  | 2502.0   | 2604.0   | 2635.0   | 2674.0   | 2680.0   | 2598.0   | 2674.2   |
| Female          | 1810.0   | 1852.0  | Euthanized on 15th Day |
|                 | 2206.0   | 2364.2  |          |          |          |          |          |          |          |
|                 | 1711.0   | 1756.0  | 1897.0   | 1924.8   | Euthanized on 29th Day |
|                 | 2098.0   | 2205.0  | 2398.0   | 2338.7   |          |          |          |          |          |
|                 | 2097.0   | 2211.6  | 2485.0   | 2512.0   |          |          |          |          |          |
|                 | 2045.0   | 2281.2  | 2626.0   | 2701.3   | 2770.0   | 2889.0   | 3012.0   | 2934.0   | 2577.0   |
|                 | 1901.0   | 2037.3  | 2293.0   | 2329.7   | 2410.0   | 2349.0   | 2547.0   | 2540.0   | 2557.0   |
|                 | 1845.0   | 1980.0  | 2129.0   | 2257.6   | 2129.0   | 2253.0   | 2339.0   | 2409.0   | 2431.0   |
|                 | 2032.0   | 2086.2  | 2271.0   | 2236.9   | 2329.0   | 2305.0   | 2394.0   | 2465.0   | 2494.4   |
|                 | 2294.0   | 2424.7  | 2648.0   | 2710.2   | 2796.0   | 2839.0   | 2937.0   | 2953.0   | 2928.2   |

(continued on next page)
| Sex                  | Baseline | 8th Day | 19th Day | 26th Day | 37th Day | 50th Day | 64th Day | 78th Day | 89th Day |
|---------------------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| Experimental Control Oral (EC–OR) |           |         |          |          |          |          |          |          |          |
| ♂                   | 1765.0   | 1949.0  |          |          |          |          |          |          |          |
|                     | 1415.0   | 1472.0  |          |          |          |          |          |          |          |
|                     | 1908.0   | 2075.0  |          |          |          |          |          |          |          |
|                     | 1955.0   | 2076.0  | 2227.0   | 2261.0   |          |          |          |          |          |
|                     | 1830.0   | 1862.0  | 2010.0   | 2017.0   |          |          |          |          |          |
|                     | 2158.0   | 2285.0  | 2515.0   | 2512.0   | 2464.0   | 2455.0   | 2497.0   | 2416.0   | 2249.0   |
|                     | 2020.0   | 2203.0  | 2237.0   | 2343.0   | 2300.0   | 2248.0   | 2299.0   | 2207.0   | 2155.0   |
|                     | 2093.0   | 2239.0  | 2290.0   | 2353.0   | 2329.0   | 2327.0   | 2424.0   | 2425.0   | 2325.0   |
|                     | 2165.0   | 2329.0  | 2529.0   | 2512.0   | 2479.0   | 2546.0   | 2637.0   | 2612.0   | 2699.0   |
|                     | 2291.0   | 2349.0  | 2535.0   | 2550.0   | 2351.0   | 2374.0   | 2298.0   | 2410.0   | 2465.5   |
| ♀                   | 2078.0   | 2162.3  |          |          |          |          |          |          |          |
|                     | 2431.0   | 2579.7  |          |          |          |          |          |          |          |
|                     | 1900.0   | 2040.8  | 2254.0   | 2342.3   |          |          |          |          |          |
|                     | 2242.0   | 2363.2  | 2699.0   | 2816.0   |          |          |          |          |          |
|                     | 1849.0   | 1953.2  | 2130.0   | 2220.1   |          |          |          |          |          |
|                     | 1948.0   | 2059.1  | 2361.0   | 2414.0   | 2496.0   | 2570.0   | 2670.0   | 2677.0   | 2763.0   |
|                     | 1945.0   | 2103.4  | 2436.0   | 2528.0   | 2500.0   | 2630.0   | 2748.0   | 2806.0   | 2793.0   |
|                     | 2056.0   | 2233.0  | 2487.0   | 2598.2   | 2556.0   | 2539.0   | 2797.0   | 2788.0   | 2845.0   |
|                     | 2146.0   | 2284.6  | 2460.0   | 2476.5   | 2441.0   | 2653.0   | 2615.0   | 2624.0   | 2521.0   |
|                     | 2217.0   | 2331.0  | 2632.0   | 2670.0   | 2650.0   | 2667.0   | 2740.0   | 2822.0   | 2829.6   |

(continued on next page)
| Sex       | Baseline | 8th Day | 19th Day | 26nd Day | 37th Day | 50th Day | 64th Day | 78th Day | 89th Day |
|-----------|----------|---------|----------|----------|----------|----------|----------|----------|---------|
| ♂         | 2033.0   | 2093.2  |          |          |          |          |          |          |         |
|           | 1763.0   | 1697.0  |          |          |          |          |          |          |         |
|           | 1986.0   | 2139.3  |          |          |          |          |          |          |         |
| 1947.0    | 2180.7   | 2381.0  | 2547.0   |          |          |          |          |          |         |
| 2256.0    | 2380.6   | 2540.0  | 2517.0   |          |          |          |          |          |         |
| 2007.0    | 2114.6   | 2212.0  | 2287.0   |          |          |          |          |          |         |
| 1915.0    | 2007.3   | 2086.0  | 2076.0   |          |          |          |          |          |         |
| 2015.0    | 2166.1   | 2301.0  | 2335.0   |          |          |          |          |          |         |
| 2162.0    | 2298.8   | 2539.0  | 2577.0   |          |          |          |          |          |         |
| 2047.0    | 2203.9   | 2356.0  | 2444.0   |          |          |          |          |          |         |
|           | 1217.4   | 1197.0  |          |          |          |          |          |          |         |
| ♂         |          |         |          |          |          |          |          |          |         |
|           | 1925.7   | 2133.0  |          |          |          |          |          |          |         |
| 1829.7    | 1988.0   | 2082.0  | 2231.1   |          |          |          |          |          |         |
| 2051.6    | 2187.0   | 2422.0  | 2335.2   |          |          |          |          |          |         |
| 1982.1    | 2115.0   | 2257.0  | 2252.5   |          |          |          |          |          |         |
| 1923.7    | 2123.0   | 2382.0  | 2466.0   |          |          |          |          |          |         |
| 1905.3    | 2117.0   | 2280.0  | 2418.3   |          |          |          |          |          |         |
| 1920.1    | 2050.0   | 2278.0  | 2334.3   |          |          |          |          |          |         |
| 2053.8    | 2120.0   | 2303.0  | 2198.4   | 1976.0   | 1787.0   | 1556.0   | 1335.0   | –        |         |
| 2126.0    | 2124.0   | 2353.0  | 2408.0   | 2395.0   | 2386.0   | 2446.0   | 2523.0   | 2535.2   |         |

Euthanized on 15th Day
Euthanized on 29th Day
Euthanized on 15th Day
(continued on next page)
| Sex  | Baseline | 8th Day | 19th Day | 26th Day | 37th Day | 50th Day | 64th Day | 78th Day | 89th Day |
|------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| ♂    | 1855.0   | 2028.5  |          |          | Euthanized on 15th Day |          |          |          |          |
|      | 1575.0   | 1653.0  |          |          |          |          |          |          |          |
|      | 2105.0   | 2175.4  |          |          |          |          |          |          |          |
|      | 1669.0   | 1705.5  | 1736.0   | 1701.0   |          | Euthanized on 29th Day |          |          |          |
|      | 2040.0   | 2207.5  | 2310.0   | 2260.0   |          |          |          |          |          |
|      | 2010.0   | 2111.3  | 2219.0   | 2300.0   | 2302.0   | 2318.0   | 2344.0   | 2466.0   | 2423.0   |
|      | 2080.0   | 2212.2  | 2360.0   | 2395.0   | 2358.0   | 2192.0   | 2658.0   | 2624.0   | 2640.0   |
|      | 2119.0   | 2240.6  | 2453.0   | 2459.0   | 2382.0   | 2402.0   | 2675.0   | 2686.0   | 2697.0   |
|      | 2011.0   | 2135.1  | 2317.0   | 2294.0   | 2202.0   | 2365.0   | 2595.0   | 2575.0   | 2538.0   |
|      | 2223.0   | 2315.7  | 2465.0   | 2559.0   | 2437.0   | 2446.0   | 2490.0   | 2504.0   | 2540.0   |
| ♂    | 1916.1   | 2122.0  |          |          | Euthanized on 15th Day |          |          |          |          |
|      | 2172.5   | 2315.0  |          |          |          |          |          |          |          |
|      | 2026.3   | 2163.0  | 2290.0   | 2351.8   |          | Euthanized on 29th Day |          |          |          |
|      | 2051.3   | 2152.0  | 2475.0   | 2556.1   |          |          |          |          |          |
|      | 2248.2   | 2357.0  | 2577.0   | 2636.1   |          |          |          |          |          |
|      | 1872.5   | 1962.0  | 2119.0   | 2182.1   | 2158.0   | 2093.0   | 1709.0   | 1802.0   | 1646.0   |
|      | 1240.0   | 1403.0  | 1755.0   | 1987.2   | 2127.0   | 2279.0   | 2452.0   | 2470.0   | 2197.2   |
|      | 1786.4   | 1862.0  | 2053.0   | 2141.3   | 2158.0   | 2290.0   | 2375.0   | 2431.0   | 2296.0   |
|      | 1965.3   | 2056.0  | 2244.0   | 2301.0   | 2349.0   | 2389.0   | 2512.0   | 2560.0   | 2553.7   |
|      | 2329.9   | 2464.0  | 2656.0   | 2785.2   | 2697.0   | 2826.0   | 2866.0   | 2867.0   | 2845.0   |

(continued on next page)
### Table 2 (continued)

| Sex | Baseline | 8th Day | 19th Day | 26th Day | 37th Day | 50th Day | 64th Day | 78th Day | 89th Day |
|-----|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| ☀️  | 1987.0   | 2174.3  | Euthanized on 15th Day |
|     | 1604.0   | 1498.0  |          |          |          |          |          |          |          |
|     | 2176.0   | 2506.3  |          |          |          |          |          |          |          |
|     | 1973.0   | 2087.9  | 2251.0   | 2283.0   |          |          |          |          |          |
|     | 2168.0   | 2338.5  | 2521.0   | 2532.0   |          |          |          |          |          |
|     | 1973.0   | 2190.7  | 2340.0   | 2344.0   | 2325.0   | 2331.0   | 2397.0   | 2457.0   | 2502.0   |
|     | 1944.0   | 2051.3  | 2145.0   | 2254.0   | 2236.0   | 2248.0   | 2381.0   | 2328.0   | 2412.0   |
|     | 1951.0   | 1999.8  | 2132.0   | 2180.0   | 2338.0   | 2213.0   | 2212.0   | 2212.0   | 2065.0   |
|     | 2092.0   | 2341.8  | 2511.0   | 2508.0   | 2492.0   | 2556.0   | 2462.0   | 2491.0   | 2487.0   |
|     | 2166.0   | 2297.8  | 2519.0   | 2541.0   | 2460.0   | 2532.0   | 2287.0   | 2298.0   | 2338.0   |
| ♂️  | 1687.4   | 1775.0  | Euthanized on 15th Day |
|     | 2162.3   | 2278.0  |          |          |          |          |          |          |          |
|     | 1745.2   | 1831.0  | 1986.0   | 2103.8   |          |          |          |          |          |
|     | 2088.8   | 2237.0  | 2450.0   | 2696.0   |          |          |          |          |          |
|     | 2162.0   | 2343.0  | 2464.0   | 2630.7   |          |          |          |          |          |
|     | 1561.3   | 1675.0  | 1873.0   | 1984.6   | 2325.0   | 2022.0   | 2140.0   | 2134.0   | 2252.6   |
|     | 1841.7   | 1982.0  | 2038.0   | 2157.3   | 2236.0   | 2218.0   | 2299.0   | 2365.0   | 2346.5   |
|     | 1967.0   | 2074.0  | 2260.0   | 2388.6   | 2338.0   | 2415.0   | 2497.0   | 2570.0   | 2536.4   |
|     | 1891.5   | 2068.0  | 2219.0   | 2325.1   | 2492.0   | 2480.0   | 2625.0   | 2657.0   | 2631.5   |
|     | 2113.1   | 2163.0  | 2312.0   | 2399.4   | 2460.0   | 2675.0   | 2777.0   | 2794.0   | 2785.0   |
**Table 3.1**
Day 15th - Haematological profile of rats exposed to recombinant HPV vaccine.

| Group                  | Time Point | Sex | RBC (10E6/mm³) | WBC (10E3/mm³) | HCT (%) | MCV (µm³) | MCH (pg) | MCHC (g/dl) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) |
|------------------------|------------|-----|----------------|----------------|---------|-----------|---------|-------------|-----------------|-----------------|---------------|----------------|
| Vehicle Control        | 15th Day   | ♂   | 17.9           | 13.19          | 46.7    | 54.1      | 20.7    | 38.2        | 637             | 13              | 82            | 4              |
|                        |            | ♀   | 18.6           | 9.87           | 46.0    | 54.6      | 20.8    | 38.2        | 778             | 18              | 76            | 5              |
| Experimental Control   | Intra-Nasal| ♂   | 18.0           | 11.15          | 47.9    | 51.7      | 19.5    | 37.6        | 628             | 15              | 80            | 4              |
|                        |            | ♀   | 13.9           | 7.03           | 34.6    | 51.4      | 20.7    | 40.2        | 1238            | 8               | 91            | 1              |
| Oral                   | 15th Day   | ♂   | 18.2           | 10.76          | 47.1    | 54.0      | 20.8    | 38.6        | 892             | 12              | 83            | 3              |
|                        |            | ♀   | 18.2           | 10.76          | 47.1    | 54.0      | 20.8    | 38.6        | 892             | 12              | 83            | 3              |
| Prophylactic Dose      | Intra-Nasal| ♂   | 18.1           | 12.01          | 48.2    | 55.0      | 20.7    | 37.7        | 943             | 18              | 78            | 3              |
|                        |            | ♀   | 17.6           | 5.55           | 46.3    | 54.9      | 20.9    | 38.1        | 881             | 45              | 49            | 4              |
| Oral                   | 15th Day   | ♂   | 17.8           | 13.52          | 45.8    | 54.0      | 20.3    | 37.6        | 966             | 12              | 82            | 5              |
|                        |            | ♀   | 18.4           | 10.32          | 48.4    | 53.6      | 20.4    | 38.1        | 1066            | 15              | 78            | 3              |
| Average Dose (Intra-Nasal)| 15th Day | ♂   | 17.8           | 12.34          | 45.7    | 55.0      | 21.4    | 38.9        | 820             | 14              | 83            | 2              |
|                        |            | ♀   | 18.1           | 9.02           | 47.3    | 55.5      | 21.2    | 38.3        | 889             | 19              | 76            | 4              |
|                        |            | ♂   | 17.0           | 9.02           | 47.3    | 55.5      | 21.2    | 38.3        | 889             | 19              | 76            | 4              |
|                        |            | ♀   | 17.9           | 10.97          | 47.3    | 55.5      | 21.2    | 38.3        | 889             | 19              | 76            | 4              |
|                        |            | ♂   | 17.0           | 10.97          | 47.3    | 55.5      | 21.2    | 38.3        | 889             | 19              | 76            | 4              |
|                        |            | ♀   | 17.9           | 10.97          | 47.3    | 55.5      | 21.2    | 38.3        | 889             | 19              | 76            | 4              |

♀: Female, ♂: Male
## Table 3.2
Day 29th - Haematological profile of rats exposed to recombinant HPV vaccine.

| Group               | Time Point | Sex | HGB (g/dl) | RBC (10E6/mm3) | WBC (10E3/mm³) | HCT (%) | MCV (μm³) | MCH (pg) | MCHC (g/dl) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) |
|---------------------|------------|-----|------------|----------------|----------------|---------|-----------|---------|-------------|----------------|----------------|--------------|----------------|
| Vehicle Control     | 29th Day   | ♂  | 14.8       | 10.4           | 4.4            | 3.3     | 3.3       | 3.0     | 3.0         | 3.0            | 3.0            | 3.0          | 3.0            |
|                     |            | ♀  | 8.2        | 6.8            | 4.6            | 3.4     | 3.0       | 2.8     | 2.8         | 2.8            | 2.8            | 2.8          | 2.8            |
| Experimental Control| Intra-Nasal| ♂  | 16.3       | 12.0           | 4.7            | 3.4     | 3.4       | 3.4     | 3.4         | 3.4            | 3.4            | 3.4          | 3.4            |
|                     |            | ♀  | 11.1       | 8.2            | 4.5            | 3.5     | 3.5       | 3.5     | 3.5         | 3.5            | 3.5            | 3.5          | 3.5            |
| Oral                | 29th Day   | ♂  | 14.8       | 10.9           | 4.3            | 3.4     | 3.2       | 3.2     | 3.2         | 3.2            | 3.2            | 3.2          | 3.2            |
|                     |            | ♀  | 13.7       | 8.6            | 4.4            | 3.3     | 3.3       | 3.3     | 3.3         | 3.3            | 3.3            | 3.3          | 3.3            |
| Prophylactic Dose   | Intra-Nasal| ♂  | 15.0       | 10.9           | 4.2            | 3.4     | 3.4       | 3.4     | 3.4         | 3.4            | 3.4            | 3.4          | 3.4            |
|                     |            | ♀  | 15.3       | 10.7           | 4.7            | 3.5     | 3.5       | 3.5     | 3.5         | 3.5            | 3.5            | 3.5          | 3.5            |
| Oral                | 29th Day   | ♂  | 14.8       | 10.9           | 4.3            | 3.4     | 3.2       | 3.2     | 3.2         | 3.2            | 3.2            | 3.2          | 3.2            |
|                     |            | ♀  | 13.7       | 8.1            | 4.3            | 3.4     | 3.4       | 3.4     | 3.4         | 3.4            | 3.4            | 3.4          | 3.4            |
| Average Dose (Intra-Nasal) | 29th Day   | ♂  | 15.0       | 10.9           | 4.3            | 3.4     | 3.4       | 3.4     | 3.4         | 3.4            | 3.4            | 3.4          | 3.4            |
|                     |            | ♀  | 13.7       | 8.1            | 4.3            | 3.4     | 3.4       | 3.4     | 3.4         | 3.4            | 3.4            | 3.4          | 3.4            |
Table 3.3
Day 93rd - Haematological profile of rats exposed to recombinant HPV vaccine.

| Group                      | Time Point | Sex | HGB (g/dl) | RBC (10E6/mm3) | WBC (10E3/mm3) | HCT (%) | MCV (µm3) | MCH (pg) | MCHC (g/dl) | PLT (10E3/mm3) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) |
|----------------------------|------------|-----|------------|----------------|----------------|---------|-----------|----------|-------------|----------------|-----------------|-----------------|---------------|----------------|
| Vehicle Control            | 93rd Day   | ♂   | 17.7       | 9.06           | 9.50           | 49.4    | 54.5      | 19.6     | 35.9        | 781             | 22              | 72              | 5              | 1              |
|                            |            | 16.8| 9.23       | 10.66          | 46.5           | 50.4    | 18.2      | 36.1     | 1039        | 30              | 65              | 4               | 1              |
|                            |            | 17.8| 9.14       | 8.41           | 48.2           | 52.7    | 19.4      | 36.9     | 956         | 28              | 68              | 3               | 1              |
|                            |            | 18.4| 9.53       | 8.86           | 50.0           | 52.5    | 19.3      | 36.7     | 1024        | 24              | 72              | 3               | 1              |
|                            |            | 20.1| 10.30      | 9.35           | 52.7           | 51.1    | 19.5      | 38.1     | 762         | 26              | 70              | 3               | 1              |
|                            |            | 18.7| 9.35       | 12.71          | 48.2           | 51.6    | 20.0      | 38.7     | 794         | 23              | 73              | 3               | 1              |
|                            |            | 17.6| 9.01       | 10.19          | 48.3           | 53.6    | 19.5      | 36.4     | 1104        | 15              | 82              | 2               | 1              |
|                            |            | 17.0| 8.52       | 6.50           | 46.8           | 54.9    | 20.0      | 36.4     | 1002        | 17              | 80              | 2               | 1              |
|                            |            | 17.3| 8.70       | 2.75           | 47.4           | 54.5    | 19.8      | 36.4     | 878         | 52              | 64              | 3               | 1              |
|                            |            | 18.5| 9.38       | 10.18          | 48.8           | 52.0    | 19.7      | 37.8     | 945         | 20              | 77              | 2               | 1              |
|                            |            | 17.3| 8.41       | 12.41          | 45.2           | 53.8    | 20.5      | 38.2     | 1021        | 24              | 72              | 3               | 1              |
|                            |            | 17.7| 9.10       | 6.67           | 46.9           | 51.6    | 19.5      | 37.7     | 1133        | 20              | 74              | 5               | 1              |
| Experimental Control       | Intra-93rd| ♂   | 19.2       | 10.03          | 9.39           | 51.5    | 51.3      | 19.1     | 37.2        | 959             | 18              | 76              | 5               | 1              |
|                            | Nasal Day  |     | 18.0       | 9.48           | 8.20           | 48.8    | 51.4      | 19.0     | 37.0        | 1299            | 18              | 73              | 8               | 1              |
|                            |            | 17.9| 9.06       | 7.63           | 48.8           | 53.9    | 19.8      | 36.7     | 1185        | 22              | 75              | 2               | 1              |
|                            |            | 18.3| 9.71       | 12.06          | 49.9           | 59.4    | 18.8      | 36.6     | 1145        | 20              | 75              | 4               | 1              |
|                            |            | 17.1| 8.68       | 11.55          | 43.2           | 49.8    | 19.7      | 39.5     | 1034        | 25              | 71              | 3               | 1              |
|                            |            | 19.0| 9.73       | 9.36           | 49.9           | 51.3    | 19.6      | 38.1     | 823         | 30              | 65              | 3               | 2              |
|                            |            | 17.1| 8.52       | 7.96           | 46.2           | 54.2    | 20.1      | 37.0     | 852         | 34              | 60              | 4               | 2              |
|                            |            | 18.2| 9.46       | 8.87           | 49.6           | 52.4    | 19.2      | 36.7     | 981         | 29              | 65              | 4               | 2              |
|                            |            | 18.0| 8.94       | 7.34           | 48.1           | 53.8    | 20.1      | 37.4     | 1060        | 17              | 80              | 2               | 1              |
|                            |            | 18.3| 9.02       | 10.40          | 47.9           | 53.1    | 20.3      | 38.1     | 859         | 20              | 76              | 3               | 1              |
|                            |            | 18.4| 9.03       | 8.17           | 47.5           | 52.6    | 20.3      | 38.7     | 840         | 19              | 76              | 4               | 1              |
|                            | Oral 93rd  | ♂   | 18.2       | 9.26           | 12.59          | 48.4    | 52.3      | 19.6     | 37.5        | 1144            | 28              | 67              | 4               | 1              |
|                            | Day       |     | 16.9       | 8.88           | 6.84           | 45.8    | 51.6      | 19.1     | 37.0        | 1056            | 35              | 58              | 5               | 2              |
|                            |            | 17.5| 9.11       | 15.37          | 48.1           | 52.8    | 19.2      | 36.5     | 951         | 25              | 70              | 4               | 1              |
|                            |            | 19.0| 9.78       | 9.68           | 48.7           | 49.8    | 19.4      | 39.0     | 802         | 35              | 61              | 3               | 1              |
|                            |            | 18.2| 9.45       | 9.28           | 47.7           | 50.5    | 19.3      | 38.2     | 885         | 26              | 69              | 3               | 2              |
|                            |            | 16.8| 8.30       | 7.74           | 44.2           | 53.3    | 20.2      | 37.9     | 1206        | 18              | 78              | 3               | 1              |
|                            |            | 17.2| 8.70       | 9.79           | 45.8           | 52.7    | 19.7      | 37.5     | 1106        | 18              | 76              | 5               | 1              |
|                            |            | 16.9| 8.40       | 7.13           | 43.8           | 52.2    | 20.2      | 38.6     | 1104        | 22              | 75              | 2               | 1              |
|                            |            | 17.0| 8.62       | 9.57           | 46.2           | 53.7    | 19.7      | 36.7     | 1110        | 20              | 77              | 2               | 1              |
|                            |            | 17.2| 8.61       | 9.56           | 47.7           | 55.3    | 20.0      | 36.2     | 964         | 15              | 82              | 2               | 1              |
|                            |            | 17.7| 8.81       | 11.80          | 47.6           | 54.1    | 20.1      | 37.2     | 887         | 19              | 77              | 3               | 1              |

(continued on next page)
## Table 3.3 (continued)

| Group | Time Point | Sex | HGB (g/dl) | RBC (10E6/μl) | WBC (10E3/μl) | HCT (%) | MCV (μm3) | MCH (pg) | MCHC (g/dl) | PLT (10E3/μl) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) |
|-------|------------|-----|------------|---------------|---------------|---------|----------|---------|-------------|---------------|----------------|----------------|--------------|--------------|
| Prophylactic Dose | Intra-Nasal | 93rd Day | ♂ | 18.6 | 7.30 | 7.73 | 51.1 | 49.6 | 18.1 | 36.5 | 864 | 27 | 68 | 3 | 2 |
| | | | ♂ | 16.9 | 8.59 | 11.45 | 45.5 | 53.0 | 19.7 | 37.1 | 883 | 25 | 68 | 5 | 2 |
| | | | ♂ | 16.4 | 8.92 | 7.39 | 44.3 | 49.6 | 19.4 | 37.1 | 874 | 35 | 58 | 5 | 2 |
| | | | ♂ | 17.7 | 9.15 | 9.27 | 45.6 | 49.8 | 19.3 | 38.8 | 1032 | 26 | 69 | 4 | 1 |
| | | | ♂ | 17.0 | 8.83 | 7.84 | 44.1 | 50.0 | 19.3 | 38.6 | 1061 | 20 | 76 | 3 | 1 |
| | | | ♂ | 16.8 | 8.67 | 9.62 | 43.4 | 50.0 | 19.4 | 38.7 | 875 | 29 | 67 | 3 | 1 |
| | | | ♂ | 17.2 | 8.63 | 6.90 | 45.0 | 52.1 | 20.0 | 38.3 | 903 | 22 | 72 | 5 | 1 |
| | | | ♂ | 17.3 | 8.68 | 8.69 | 46.4 | 53.4 | 19.9 | 37.2 | 947 | 32 | 65 | 2 | 1 |
| | | | ♂ | 17.4 | 8.69 | 7.27 | 47.2 | 54.3 | 20.0 | 36.8 | 902 | 35 | 61 | 3 | 1 |
| | Oral | 93rd Day | ♂ | 16.9 | 8.91 | 7.19 | 45.7 | 51.3 | 19.0 | 36.9 | 794 | 27 | 63 | 8 | 2 |
| | | | ♂ | 17.7 | 9.45 | 11.16 | 48.9 | 51.8 | 18.8 | 36.3 | 758 | 29 | 64 | 5 | 2 |
| | | | ♂ | 18.0 | 9.17 | 5.03 | 46.2 | 50.3 | 19.7 | 39.1 | 802 | 28 | 65 | 5 | 2 |
| | | | ♂ | 17.1 | 8.95 | 9.05 | 44.4 | 49.6 | 19.2 | 38.6 | 786 | 26 | 68 | 4 | 2 |
| | | | ♂ | 16.8 | 8.57 | 8.66 | 48.2 | 56.3 | 19.7 | 35.1 | 222 | 25 | 69 | 4 | 2 |
| | | | ♂ | 16.3 | 8.84 | 5.32 | 43.0 | 48.6 | 18.4 | 37.9 | 791 | 35 | 57 | 6 | 2 |
| | | | ♂ | 17.4 | 8.70 | 6.37 | 46.8 | 53.8 | 20.1 | 37.3 | 897 | 26 | 70 | 3 | 1 |
| | | | ♂ | 17.4 | 8.76 | 7.40 | 47.3 | 54.0 | 19.9 | 36.8 | 847 | 27 | 68 | 3 | 2 |
| | | | ♂ | 18.0 | 8.97 | 8.15 | 48.3 | 50.2 | 20.0 | 37.2 | 799 | 26 | 70 | 3 | 1 |
| | | | ♂ | 16.8 | 8.46 | 4.92 | 44.2 | 52.3 | 19.8 | 37.9 | 920 | 28 | 68 | 2 | 2 |
| | | | ♂ | 16.8 | 8.62 | 6.51 | 43.9 | 50.9 | 19.5 | 38.2 | 976 | 20 | 75 | 4 | 1 |
| | | | ♂ | 16.6 | 8.10 | 8.93 | 40.9 | 50.5 | 20.5 | 40.7 | 1271 | 28 | 68 | 3 | 1 |
| | Average Dose (Intra-Nasal) | 93rd Day | ♂ | 19.9 | 10.33 | 8.86 | 54.5 | 52.8 | 19.3 | 36.6 | 792 | 27 | 65 | 6 | 2 |
| | | | ♂ | 18.7 | 9.34 | 11.38 | 49.1 | 52.5 | 20.0 | 38.2 | 956 | 21 | 73 | 6 | 0 |
| | | | ♂ | 17.2 | 9.22 | 7.78 | 45.4 | 49.2 | 18.7 | 37.9 | 977 | 22 | 72 | 5 | 1 |
| | | | ♂ | 17.3 | 9.40 | 9.94 | 45.6 | 48.5 | 18.4 | 38.0 | 940 | 20 | 72 | 6 | 2 |
| | | | ♂ | 17.5 | 9.08 | 10.88 | 46.4 | 51.1 | 19.2 | 37.7 | 864 | 20 | 73 | 5 | 2 |
| | | | ♂ | 18.0 | 9.38 | 8.52 | 47.4 | 50.5 | 19.2 | 37.9 | 922 | 21 | 73 | 5 | 1 |
| | | | ♂ | 13.3 | 6.58 | 10.89 | 35.6 | 54.0 | 20.3 | 37.5 | 1445 | 20 | 74 | 5 | 1 |
| | | | ♂ | 17.2 | 8.75 | 11.99 | 44.8 | 51.2 | 19.6 | 38.3 | 848 | 25 | 69 | 5 | 1 |
| | | | ♂ | 15.9 | 8.00 | 9.83 | 40.0 | 50.0 | 19.9 | 39.7 | 915 | 18 | 78 | 4 | 0 |
| | | | ♂ | 17.3 | 8.64 | 13.53 | 46.4 | 53.8 | 20.1 | 37.4 | 819 | 23 | 75 | 2 | 0 |
| | | | ♂ | 18.0 | 9.21 | 7.33 | 49.0 | 53.2 | 15.5 | 36.7 | 843 | 25 | 71 | 2 | 2 |
| | | | ♂ | 17.3 | 3.57 | 13.97 | 47.4 | 55.3 | 20.2 | 36.6 | 942 | 18 | 79 | 2 | 1 |
### Table 4.1
Day 15th - Haematological profile of rabbits exposed to recombinant HPV vaccine.

| Group                     | Time Point | Sex | HGB (g/dl) | RBC (10E6/mm3) | WBC (10E3/mm3) | HCT (%) | MCV (µm3) | MCH (pg) | MCHC (g/dl) | PLT (10E3/mm3) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Basophils (%) |
|---------------------------|------------|-----|------------|----------------|----------------|---------|-----------|----------|-------------|----------------|----------------|----------------|--------------|----------------|--------------|
| Vehicle Control           | 15th Day   | ♂   | 12.9       | 6.15           | 6.45            | 38.4    | 62.5      | 20.9     | 33.5        | 727            | 15             | 78             | 4            | 1             | 2            |
|                           |            | ♀   | 15.0       | 6.89           | 11.07           | 44.2    | 64.2      | 21.8     | 34.0        | 251            | 20             | 73             | 3            | 2             | 2            |
|                           |            |     | 16.3       | 7.34           | 14.65           | 44.4    | 60.5      | 22.2     | 36.7        | 627            | 35             | 55             | 5            | 2             | 3            |
|                           |            | ♂   | 12.9       | 6.15           | 12.28           | 36.6    | 59.5      | 21.0     | 35.3        | 1050           | 48             | 46             | 4            | 0             | 2            |
|                           |            | ♀   | 14.5       | 6.28           | 10.84           | 38.0    | 60.5      | 23.1     | 38.1        | 782            | 25             | 70             | 2            | 1             | 2            |
| Experimental Control      | IN         | ♂   | 13.4       | 5.84           | 10.13           | 38.5    | 65.9      | 23.0     | 34.8        | 1179           | 45             | 49             | 4            | 1             | 1            |
|                           | 15th Day   | ♀   | 14.6       | 5.81           | 10.68           | 37.7    | 64.9      | 25.1     | 38.6        | 1566           | 24             | 69             | 3            | 1             | 3            |
|                           |            |     | 12.3       | 5.13           | 11.48           | 31.3    | 61.1      | 24.0     | 39.2        | 972            | 30             | 65             | 4            | 0             | 1            |
|                           |            | ♂   | 15.9       | 7.22           | 4.84            | 43.7    | 60.6      | 22.0     | 36.3        | 627            | 30             | 62             | 4            | 2             | 2            |
|                           |            | ♀   | 11.3       | 5.22           | 17.27           | 32.5    | 62.2      | 21.6     | 34.8        | 1566           | 24             | 69             | 3            | 1             | 3            |
|                           |            |     | 17.0       | 7.45           | 8.09            | 46.9    | 62.9      | 22.8     | 36.2        | 615            | 20             | 74             | 4            | 1             | 1            |
|                           |            | ♂   | 13.9       | 6.18           | 8.88            | 36.7    | 59.3      | 22.5     | 37.9        | 1769           | 22             | 70             | 4            | 1             | 3            |
|                           |            | ♀   | 14.2       | 6.19           | 8.08            | 38.9    | 62.8      | 23.0     | 36.6        | 698            | 22             | 71             | 3            | 1             | 3            |
| Prophylactic Dose (PD)    | IN         | ♂   | 14.2       | 6.07           | 9.77            | 40.1    | 66.1      | 23.4     | 35.4        | 752            | 27             | 66             | 5            | 1             | 1            |
|                           | 15th Day   | ♀   | 13.7       | 6.14           | 7.07            | 40.1    | 65.4      | 22.2     | 34.0        | 1619           | 62             | 32             | 2            | 1             | 1            |
|                           |            |     | 15.9       | 7.24           | 10.38           | 45.7    | 63.1      | 21.9     | 34.8        | 824            | 20             | 75             | 2            | 1             | 2            |
|                           |            | ♂   | 16.6       | 8.07           | 5.18            | 45.2    | 56.0      | 20.6     | 36.8        | 344            | 37             | 55             | 5            | 1             | 2            |
|                           |            | ♀   | 13.7       | 5.75           | 8.53            | 37.0    | 64.3      | 23.8     | 37.0        | 998            | 25             | 70             | 2            | 1             | 2            |
|                           |            |     | 14.5       | 6.26           | 10.81           | 42.3    | 67.5      | 23.2     | 34.4        | 682            | 30             | 64             | 3            | 1             | 2            |
|                           |            | ♂   | 15.4       | 6.35           | 8.46            | 40.9    | 64.5      | 24.2     | 37.5        | 657            | 20             | 75             | 3            | 1             | 1            |
|                           |            | ♀   | 16.0       | 7.46           | 9.31            | 44.2    | 59.3      | 21.4     | 36.1        | 480            | 22             | 70             | 4            | 2             | 2            |
|                           |            |     | 14.9       | 6.09           | 10.86           | 37.7    | 61.9      | 22.9     | 37.0        | 712            | 18             | 75             | 5            | 1             | 1            |
|                           |            | ♂   | 14.7       | 6.13           | 6.07            | 39.6    | 64.7      | 23.9     | 37.0        | 642            | 18             | 76             | 2            | 1             | 3            |
|                           |            | ♀   | 15.9       | 7.04           | 8.77            | 45.6    | 64.7      | 22.6     | 34.9        | 563            | 30             | 64             | 3            | 1             | 2            |
| Average Dose (IN)         | 15th Day   | ♂   | 12.8       | 5.96           | 4.71            | 36.3    | 60.9      | 21.5     | 35.2        | 1811           | 55             | 40             | 3            | 1             | 1            |
|                           |            | ♀   | 14.4       | 6.34           | 9.72            | 37.0    | 58.4      | 22.8     | 39.0        | 540            | 25             | 69             | 2            | 1             | 3            |
|                           |            |     | 14.4       | 6.16           | 12.64           | 39.8    | 64.6      | 23.4     | 36.2        | 594            | 35             | 57             | 5            | 1             | 2            |
|                           |            | ♂   | 13.3       | 5.94           | 8.27            | 36.1    | 60.8      | 22.4     | 36.9        | 925            | 25             | 70             | 2            | 1             | 2            |
| Group               | Time Point | Sex | HGB (g/dl) | RBC (10E6/mm³) | WBC (10E3/mm³) | HCT (%) | MCV (μm³) | MCH (pg) | MCHC (g/dl) | PLT (10E3/mm³) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Basophils (%) |
|---------------------|------------|-----|------------|----------------|----------------|---------|-----------|---------|------------|----------------|----------------|----------------|--------------|----------------|--------------|
| Vehicle Control     | 29th Day ♀ | 15.9 | 7.58      | 12.93         | 44.1           | 58.2    | 20.9      | 36.0    | 1071       | 30             | 62             | 5              | 2            | 1              |
|                     |            | 15.0 | 6.12      | 8.95          | 40.2           | 65.7    | 24.5      | 37.3    | 546        | 35             | 58             | 3              | 2            | 2              |
|                     |            | 14.6 | 6.28      | 8.27          | 39.4           | 62.8    | 23.3      | 37.1    | 511        | 23             | 70             | 4              | 1            | 2              |
|                     |            | 15.1 | 6.41      | 9.35          | 40.5           | 63.2    | 23.6      | 37.4    | 629        | 24             | 70             | 3              | 1            | 2              |
|                     |            | 15.4 | 6.36      | 12.70         | 40.6           | 63.8    | 24.2      | 37.9    | 539        | 15             | 78             | 4              | 1            | 2              |
| Experimental Control | IN        | 29th Day ♀ | 15.3 | 6.87      | 9.16          | 42.3    | 61.6      | 22.2    | 36.0       | 355            | 18             | 75             | 4            | 2              |
|                     |            | 17.0 | 7.43      | 9.19          | 46.7          | 62.8    | 22.9      | 36.5    | 508        | 25             | 69             | 3              | 1            | 2              |
|                     |            | 14.2 | 6.25      | 12.72         | 37.1          | 59.3    | 22.7      | 38.2    | 568        | 15             | 79             | 3              | 1            | 2              |
|                     |            | 13.1 | 6.59      | 18.80         | 36.2          | 63.6    | 23.0      | 36.2    | 925        | 50             | 41             | 6              | 1            | 2              |
|                     |            | 14.3 | 6.32      | 5.22          | 37.2          | 58.8    | 22.6      | 38.4    | 276        | 19             | 75             | 3              | 1            | 2              |
| Oral                | 29th Day ♀ | 14.9 | 7.26      | 13.36         | 40.4          | 55.7    | 20.5      | 36.9    | 739        | 30             | 62             | 6              | 1            | 1              |
|                     |            | 15.1 | 6.87      | 11.30         | 41.8          | 60.8    | 21.9      | 36.1    | 648        | 35             | 57             | 6              | 0            | 2              |
|                     |            | 16.2 | 6.84      | 7.22          | 43.3          | 63.3    | 23.7      | 37.4    | 468        | 25             | 70             | 2              | 1            | 2              |
|                     |            | 13.1 | 5.08      | 9.47          | 34.5          | 67.8    | 25.8      | 38.1    | 662        | 25             | 69             | 4              | 0            | 2              |
|                     |            | 16.3 | 7.07      | 8.52          | 44.8          | 63.3    | 23.1      | 36.4    | 699        | 25             | 70             | 2              | 1            | 2              |
| ProphylactidN Dose (PD) | 29th Day ♀ | 14.4 | 6.38      | 12.47         | 39.1          | 61.3    | 22.6      | 36.9    | 721        | 35             | 58             | 4              | 1            | 2              |
|                     |            | 16.5 | 7.04      | 8.71          | 45.9          | 65.2    | 23.5      | 36.1    | 806        | 37             | 55             | 5              | 2            | 1              |
|                     |            | 16.3 | 6.59      | 10.59         | 44.1          | 66.9    | 24.7      | 36.9    | 744        | 20             | 75             | 2              | 1            | 2              |
|                     |            | 13.4 | 5.97      | 17.55         | 34.8          | 58.4    | 22.4      | 38.4    | 747        | 26             | 68             | 3              | 1            | 2              |
|                     |            | 15.4 | 6.61      | 6.95          | 40.4          | 61.2    | 23.2      | 38.0    | 662        | 13             | 80             | 4              | 1            | 2              |
| Oral                | 29th Day ♀ | 15.1 | 6.77      | 15.96         | 41.0          | 60.5    | 22.3      | 36.9    | 1054       | 58             | 38             | 2              | 0            | 2              |
|                     |            | 15.0 | 6.67      | 12.07         | 40.2          | 60.3    | 22.4      | 37.3    | 941        | 38             | 56             | 4              | 1            | 1              |
|                     |            | 15.6 | 6.68      | 10.49         | 42.2          | 63.1    | 23.4      | 37.0    | 524        | 25             | 69             | 4              | 1            | 1              |
|                     |            | 17.0 | 6.66      | 7.50          | 45.1          | 67.8    | 25.6      | 37.8    | 544        | 12             | 82             | 3              | 1            | 2              |
|                     |            | 13.6 | 5.76      | 10.99         | 34.5          | 59.9    | 23.5      | 39.3    | 713        | 35             | 57             | 5              | 1            | 2              |
| Average Dose (IN)   | 29th Day ♀ | 16.1 | 6.65      | 11.04         | 44.6          | 67.1    | 24.1      | 36.0    | 876        | 30             | 64             | 4              | 1            | 1              |
|                     |            | 15.1 | 6.18      | 8.22          | 39.8          | 64.4    | 24.4      | 38.0    | 657        | 40             | 53             | 5              | 1            | 1              |
|                     |            | 14.9 | 6.27      | 10.73         | 39.0          | 62.2    | 23.7      | 38.2    | 412        | 20             | 72             | 4              | 2            | 2              |
|                     |            | 13.8 | 5.76      | 8.74          | 37.0          | 64.2    | 23.9      | 37.3    | 359        | 19             | 74             | 4              | 1            | 2              |
|                     |            | 14.5 | 5.76      | 11.64         | 36.8          | 63.8    | 25.1      | 39.3    | 672        | 22             | 70             | 3              | 1            | 4              |
Table 4.3
Day 93rd - Haematological profile of rabbits exposed to recombinant HPV vaccine.

| Group          | Time Point | Sex | HGB (g/dl) | RBC (10E6/μL) | WBC (10E3/mm³) | HCT (%) | MCV (μm³) | MCH (pg) | MCHC (g/dl) | PLT (10E9/μL) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Basophils (%) |
|----------------|------------|-----|------------|---------------|----------------|---------|-----------|----------|-------------|---------------|----------------|----------------|---------------|-----------------|--------------|
| Vehicle Control| 93rd Day   | ♂   | 14.5       | 6.40          | 16.31          | 41.5    | 64.8      | 22.6     | 34.9        | 679           | 35             | 60             | 2             | 1               | 2             |
|               |            | ♀   | 15.6       | 7.27          | 9.15           | 46.0    | 63.3      | 21.4     | 33.9        | 690           | 32             | 62             | 2             | 2               | 2             |
|               |            | ♂   | 16.8       | 3.35          | 12.11          | 22.5    | 67.2      | 20.2     | 30.0        | 2000          | 40             | 52             | 5             | 1               | 2             |
|               |            | ♀   | 14.4       | 6.79          | 10.65          | 40.5    | 59.7      | 21.3     | 35.6        | 526           | 65             | 30             | 2             | 1               | 2             |
|               |            | ♂   | 15.5       | 6.89          | 9.03           | 44.9    | 65.2      | 22.5     | 34.6        | 512           | 20             | 75             | 2             | 1               | 2             |
|               |            | ♀   | 13.2       | 6.10          | 8.67           | 38.4    | 63.0      | 21.7     | 34.4        | 691           | 38             | 55             | 3             | 2               | 2             |
|               |            | ♂   | 13.9       | 6.26          | 8.63           | 42.0    | 67.1      | 22.2     | 33.1        | 212           | 24             | 49             | 3             | 1               | 2             |
|               |            | ♀   | 14.9       | 6.43          | 9.64           | 42.1    | 65.5      | 23.2     | 35.5        | 571           | 25             | 66             | 5             | 1               | 3             |
|               |            | ♂   | 13.6       | 6.04          | 8.89           | 40.5    | 67.1      | 22.4     | 33.5        | 572           | 20             | 75             | 2             | 1               | 2             |
|               |            | ♀   | 16.9       | 7.59          | 9.79           | 48.9    | 64.3      | 22.3     | 34.6        | 539           | 22             | 70             | 3             | 2               | 3             |
| Experimental  | IN 93rd Day| ♂   | 14.8       | 6.78          | 6.99           | 41.5    | 61.2      | 21.9     | 35.7        | 480           | 22             | 72             | 2             | 1               | 3             |
| Control       |            | ♀   | 15.7       | 6.92          | 12.71          | 45.4    | 65.6      | 22.7     | 34.5        | 408           | 60             | 35             | 2             | 1               | 2             |
|               |            | ♂   | 15.3       | 6.58          | 7.80           | 44.5    | 67.6      | 23.3     | 34.4        | 446           | 30             | 65             | 3             | 1               | 1             |
|               |            | ♀   | 12.4       | 5.26          | 20.21          | 35.2    | 66.9      | 23.6     | 35.2        | 877           | 49             | 44             | 5             | 0               | 2             |
|               |            | ♂   | 13.4       | 6.32          | 8.17           | 39.7    | 62.7      | 21.2     | 33.7        | 715           | 40             | 55             | 2             | 1               | 2             |
|               |            | ♀   | 11.0       | 4.85          | 10.53          | 33.8    | 69.8      | 22.6     | 32.4        | 1288          | 55             | 39             | 3             | 1               | 2             |
|               |            | ♂   | 14.3       | 6.23          | 7.73           | 40.9    | 65.6      | 22.9     | 35.0        | 372           | 35             | 57             | 2             | 2               | 4             |
|               |            | ♀   | 13.1       | 5.96          | 8.91           | 37.7    | 63.2      | 22.0     | 34.7        | 534           | 22             | 70             | 4             | 1               | 3             |
| Oral 93rd Day |            | ♂   | 14.9       | 7.16          | 7.45           | 42.0    | 58.6      | 20.9     | 35.6        | 464           | 35             | 58             | 2             | 2               | 3             |
|               |            | ♀   | 14.1       | 6.47          | 10.21          | 41.7    | 64.4      | 21.8     | 33.9        | 541           | 17             | 78             | 1             | 1               | 3             |
|               |            | ♂   | 10.5       | 5.06          | 8.81           | 33.6    | 66.5      | 20.7     | 31.1        | 1432          | 40             | 50             | 6             | 2               | 2             |
|               |            | ♀   | 12.1       | 5.89          | 8.40           | 36.8    | 62.4      | 20.6     | 33.0        | 1506          | 45             | 48             | 5             | 1               | 1             |
|               |            | ♂   | 15.0       | 6.86          | 8.64           | 45.5    | 66.3      | 21.8     | 32.9        | 457           | 16             | 80             | 1             | 1               | 2             |
|               |            | ♀   | 16.7       | 7.34          | 11.36          | 52.0    | 70.8      | 22.7     | 32.0        | 177           | 15             | 80             | 2             | 1               | 2             |
|               |            | ♂   | 15.7       | 7.00          | 6.59           | 46.0    | 65.7      | 22.5     | 34.2        | 417           | 28             | 66             | 2             | 1               | 3             |
|               |            | ♀   | 13.2       | 6.02          | 38.0           | 63.2    | 21.9     | 34.7     | 826         | 70            | 22             | 4              | 4             | 1               | 3             |

(continued on next page)
| Group               | Time Point | Sex | HGB (g/dl) | RBC (10E6/mm³) | WBC (10E3/mm³) | HCT (%) | MCV (µm³) | MCH (pg) | MCHC (g/dl) | PLT (10E3/mm³) | Neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Eosinophils (%) | Basophils (%) |
|---------------------|------------|-----|------------|----------------|----------------|---------|-----------|----------|------------|----------------|----------------|----------------|-------------|---------------|--------------|--------------|
| Prophylactic IN     | 93rd Day   | ♀   | 15.1       | 6.61           | 11.73          | 40.9    | 61.8      | 22.8    | 36.9       | 446            | 30             | 63             | 4           | 1             | 2            |
|                     |            | ♂   | 13.6       | 6.45           | 5.71           | 41.5    | 64.3      | 21.1    | 32.9       | 1061           | 40             | 52             | 5           | 2             | 1            |
|                     |            | ♀   | 14.1       | 6.68           | 8.21           | 40.9    | 61.2      | 21.1    | 34.5       | 620            | 30             | 63             | 3           | 2             | 2            |
|                     |            | ♂   | 15.2       | 6.53           | 6.91           | 45.4    | 66.4      | 22.3    | 33.5       | 457            | 18             | 78             | 2           | 1             | 1            |
|                     |            | ♀   | 12.6       | 6.06           | 7.01           | 34.8    | 57.4      | 20.8    | 36.2       | 681            | 30             | 64             | 2           | 1             | 3            |
|                     |            | ♂   | 15.3       | 6.65           | 21.58          | 44.4    | 66.8      | 22.9    | 34.3       | 825            | 50             | 41             | 5           | 1             | 3            |
| Oral               | 93rd Day   | ♀   | 12.4       | 6.22           | 3.88           | 37.2    | 59.9      | 20.0    | 33.4       | 661            | 43             | 47             | 6           | 2             | 2            |
|                     |            | ♂   | 14.8       | 6.81           | 7.02           | 42.4    | 62.3      | 21.7    | 34.9       | 462            | 20             | 72             | 2           | 2             | 4            |
|                     |            | ♀   | 12.3       | 5.46           | 9.92           | 34.4    | 63.0      | 22.5    | 35.7       | 598            | 40             | 54             | 3           | 1             | 2            |
|                     |            | ♂   | 13.7       | 6.27           | 7.52           | 40.2    | 64.1      | 21.8    | 34.0       | 602            | 25             | 68             | 2           | 3             | 2            |
|                     |            | ♀   | 12.8       | 5.70           | 13.25          | 38.6    | 67.8      | 22.5    | 33.2       | 1099           | 50             | 44             | 3           | 1             | 2            |
|                     |            | ♂   | 14.5       | 6.51           | 9.45           | 40.7    | 62.5      | 22.4    | 35.7       | 476            | 20             | 75             | 2           | 1             | 2            |
|                     |            | ♀   | 14.6       | 6.74           | 8.57           | 42.1    | 62.5      | 21.7    | 34.7       | 638            | 31             | 65             | 2           | 1             | 1            |
|                     |            | ♂   | 16.1       | 7.44           | 6.69           | 45.3    | 61.0      | 21.7    | 35.5       | 554            | 22             | 72             | 2           | 2             | 2            |
|                     |            | ♀   | 11.7       | 5.82           | 12.08          | 34.9    | 60.0      | 20.2    | 33.6       | 909            | 50             | 43             | 5           | 1             | 1            |
|                     |            | ♂   | 9.3        | 4.78           | 17.45          | 28.4    | 59.3      | 19.5    | 32.8       | 1206           | 48             | 45             | 5           | 1             | 1            |
|                     |            | ♀   | 14.5       | 6.24           | 10.05          | 40.5    | 64.9      | 23.2    | 35.8       | 561            | 25             | 69             | 2           | 1             | 3            |
|                     |            | ♂   | 13.5       | 5.95           | 7.74           | 38.1    | 64.1      | 22.7    | 35.4       | 374            | 26             | 67             | 2           | 2             | 3            |
|                     |            | ♀   | 13.4       | 5.77           | 7.44           | 38.1    | 66.1      | 23.2    | 35.1       | 694            | 20             | 74             | 1           | 4             | 1            |
| Average Dose (IN)  | 93rd Day   | ♀   | 14.7       | 6.43           | 8.51           | 41.2    | 64.0      | 22.8    | 35.6       | 371            | 20             | 69             | 4           | 2             | 5            |
|                     |            | ♂   | 15.0       | 6.74           | 11.33          | 42.7    | 63.3      | 22.2    | 35.1       | 598            | 35             | 60             | 2           | 1             | 2            |
|                     |            | ♀   | 12.0       | 5.53           | 11.20          | 35.5    | 64.2      | 21.7    | 33.7       | 1532           | 48             | 43             | 5           | 2             | 2            |
|                     |            | ♂   | 13.3       | 6.04           | 9.35           | 38.3    | 63.4      | 22.0    | 34.6       | 902            | 36             | 55             | 5           | 1             | 3            |
|                     |            | ♀   | 13.3       | 6.13           | 9.58           | 37.5    | 61.2      | 21.6    | 35.4       | 584            | 36             | 59             | 2           | 1             | 2            |
|                     |            | ♂   | 16.4       | 7.90           | 11.67          | 50.6    | 64.1      | 20.7    | 32.4       | 727            | 38             | 52             | 4           | 3             | 3            |
|                     |            | ♀   | 13.8       | 5.89           | 7.02           | 38.5    | 65.3      | 23.4    | 35.8       | 504            | 28             | 65             | 3           | 1             | 3            |
|                     |            | ♂   | 14.7       | 6.57           | 8.52           | 42.7    | 65.0      | 22.4    | 34.5       | 608            | 18             | 74             | 2           | 2             | 4            |
|                     |            | ♀   | 13.3       | 6.08           | 8.92           | 39.7    | 65.3      | 22.0    | 33.6       | 789            | 29             | 65             | 2           | 2             | 2            |
|                     |            | ♂   | 14.2       | 6.24           | 8.71           | 42.5    | 68.1      | 22.7    | 33.4       | 421            | 20             | 72             | 2           | 2             | 4            |
Table 5
Biochemical profile of rats administered with rSt.HPV.

| Group             | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|-------------------|-------------------|-----|-----------|-----------|-----------|--------------------|-------------------------|--------------|-----------------|-----------------|----------------------|-----------------|
| Vehicle Control   | 15th Day          | ♂   | 48        | 99        | 366       | 0.9                | 0.1                     | 40.0         | 90.0           | 10.5            | 5.9                  | 3.9             |
|                   |                   |     | 45        | 99        | 309       | 0.9                | 0.1                     | 43.0         | 107.0          | 10.2            | 5.5                  | 3.8             |
|                   |                   | ♂   | 42        | 93        | 360       | 0.8                | 0.1                     | 41.0         | 74.0           | 10.9            | 5.6                  | 3.8             |
|                   |                   |     | 42        | 120       | 195       | 0.9                | 0.2                     | 38.0         | 85.0           | 10.6            | 5.7                  | 3.6             |
|                   | 29th Day          | ♂   | 42        | 108       | 231       | 0.9                | 0.3                     | 51.0         | 89.0           | 10.7            | 5.8                  | 3.8             |
|                   |                   |     | 42        | 108       | 252       | 0.8                | 0.2                     | 41.0         | 67.0           | 11.2            | 6.1                  | 3.9             |
|                   |                   | ♂   | 42        | 138       | 342       | 0.8                | 0.2                     | 26.0         | 96.0           | 12.0            | 7.1                  | 4.2             |
|                   |                   |     | 42        | 111       | 303       | 0.8                | 0.1                     | 32.0         | 103.0          | 13.4            | 6.6                  | 4.0             |
|                   |                   | ♂   | 45        | 102       | 321       | 0.7                | 0.2                     | 22.0         | 88.0           | 12.0            | 7.0                  | 3.9             |
|                   |                   |     | 51        | 105       | 249       | 0.8                | 0.2                     | 29.0         | 110.0          | 11.7            | 7.0                  | 4.1             |
|                   |                   | ♂   | 51        | 114       | 219       | 0.8                | 0.1                     | 25.0         | 93.0           | 11.8            | 6.7                  | 4.3             |
|                   |                   |     | 42        | 84        | 186       | 0.6                | 0.2                     | 43.0         | 79.0           | 12.7            | 7.5                  | 4.2             |
|                   | 93rd Day          | ♂   | 87        | 144       | 270       | 0.8                | 0.2                     | 29.0         | 95.0           | 9.7             | 6.7                  | 3.4             |
|                   |                   |     | 84        | 141       | 276       | 1.0                | 0.2                     | 32.0         | 127.0          | 9.9             | 6.6                  | 3.2             |
|                   |                   | ♂   | 66        | 126       | 228       | 1.1                | 0.2                     | 35.0         | 89.0           | 10.2            | 7.3                  | 3.5             |
|                   |                   |     | 81        | 135       | 333       | 0.7                | 0.2                     | 37.0         | 115.0          | 10.8            | 7.4                  | 3.7             |
|                   |                   | ♂   | 80        | 162       | 201       | 0.9                | 0.3                     | 33.0         | 145.0          | 10.9            | 6.9                  | 3.7             |
|                   |                   |     | 87        | 222       | 135       | 1.2                | 0.6                     | 42.0         | 106.0          | 10.0            | 6.6                  | 3.3             |
|                   |                   | ♂   | 81        | 162       | 159       | 1.1                | 0.2                     | 30.0         | 75.0           | 10.3            | 6.7                  | 3.5             |
|                   |                   |     | 72        | 132       | 213       | 1.1                | 0.2                     | 37.0         | 88.0           | 10.1            | 7.2                  | 3.8             |
|                   |                   | ♂   | 54        | 183       | 120       | 0.9                | 0.3                     | 36.0         | 117.0          | 12.0            | 7.3                  | 3.9             |
|                   |                   |     | 36        | 117       | 126       | 0.8                | 0.2                     | 45.0         | 109.0          | 11.7            | 6.9                  | 3.8             |
|                   |                   | ♂   | 27        | 102       | 108       | 0.8                | 0.2                     | 34.0         | 104.0          | 11.8            | 7.9                  | 4.2             |

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| Group                  | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|------------------------|------------------|-----|-----------|-----------|-----------|-------------------|------------------------|-------------|----------------|-----------------|----------------------|----------------|
| Experimental Control   | 15th Day         | ♂   | 54        | 108       | 327       | 0.8               | 0.1                    | 42.0        | 95.0           | 11.3            | 5.4                  | 3.6             |
|                        |                  | ♂   | 60        | 108       | 294       | 0.8               | 0.1                    | 51.0        | 112.0          | 10.8            | 6.4                  | 4.2             |
|                        |                  | ♂   | 33        | 60        | 246       | 0.8               | 0.2                    | 42.0        | 87.0           | 11.1            | 5.6                  | 3.5             |
|                        |                  | ♂   | 51        | 111       | 282       | 0.9               | 0.2                    | 41.0        | 76.0           | 10.8            | 5.8                  | 3.7             |
|                        |                  | ♂   | 27        | 117       | 192       | 0.7               | 0.2                    | 44.0        | 67.0           | 10.4            | 6.0                  | 3.9             |
|                        |                  | ♂   | 57        | 129       | 231       | 0.6               | 0.1                    | 39.0        | 77.0           | 10.2            | 5.8                  | 3.6             |
|                        |                  | ♀   | 45        | 99        | 279       | 0.6               | 0.2                    | 28.0        | 92.0           | 11.9            | 6.6                  | 4.1             |
|                        |                  | ♂   | 60        | 105       | 327       | 0.5               | 0.2                    | 20.0        | 77.0           | 12.0            | 6.4                  | 3.8             |
|                        |                  | ♂   | 57        | 126       | 270       | 1.0               | 0.3                    | 26.0        | 107.0          | 11.4            | 6.5                  | 4.1             |
|                        |                  | ♀   | 36        | 96        | 186       | 0.8               | 0.2                    | 34.0        | 94.0           | 12.2            | 7.5                  | 4.2             |
|                        |                  | ♂   | 39        | 105       | 180       | 0.7               | 0.2                    | 47.0        | 84.0           | 11.9            | 7.1                  | 4.2             |
|                        |                  | ♀   | 42        | 105       | 180       | 0.7               | 0.1                    | 29.0        | 89.0           | 12.1            | 6.3                  | 4.1             |
|                        |                  | ♂   | 45        | 114       | 222       | 1.3               | 0.2                    | 34.0        | 113.0          | 10.5            | 7.6                  | 3.5             |
|                        |                  | ♂   | 93        | 153       | 276       | 1.1               | 0.2                    | 32.0        | 121.0          | 9.3             | 6.8                  | 3.6             |
|                        |                  | ♂   | 90        | 159       | 228       | 1.2               | 0.2                    | 31.0        | 87.0           | 10.8            | 7.3                  | 3.7             |
|                        |                  | ♂   | 75        | 132       | 213       | 1.0               | 0.2                    | 30.0        | 88.0           | 10.7            | 7.6                  | 3.5             |
|                        |                  | ♂   | 75        | 171       | 174       | 1.0               | 0.2                    | 41.0        | 80.0           | 11.4            | 7.5                  | 3.5             |
|                        |                  | ♂   | 120       | 177       | 234       | 0.9               | 0.3                    | 32.0        | 88.0           | 10.2            | 7.2                  | 3.3             |
|                        |                  | ♀   | 60        | 153       | 204       | 1.1               | 0.2                    | 36.0        | 87.0           | 11.1            | 7.1                  | 3.7             |
|                        |                  | ♀   | 108       | 255       | 210       | 1.0               | 0.2                    | 39.0        | 92.0           | 10.3            | 7.5                  | 3.9             |
|                        |                  | ♂   | 60        | 132       | 144       | 0.9               | 0.2                    | 27.0        | 60.0           | 10.6            | 6.9                  | 3.8             |
|                        |                  | ♂   | 52        | 132       | 165       | 0.9               | 0.3                    | 32.0        | 106.0          | 11.2            | 7.3                  | 4.1             |
|                        |                  | ♂   | 45        | 111       | 129       | 0.7               | 0.3                    | 40.0        | 93.0           | 11.8            | 7.9                  | 4.4             |

(continued on next page)
Table 5 (continued)

| Group                  | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|------------------------|-------------------|-----|-----------|-----------|-----------|-------------------|------------------------|--------------|----------------|------------------|---------------------|-----------------|
| Experimental           | 15th Day          | ♂   | 57        | 99        | 318       | 0.7               | 0.1                    | 44.0         | 94.0           | 10.7             | 5.9                 | 3.9             |
| Control Oral           | (EC–OR)           |     | 63        | 111       | 312       | 0.7               | 0.1                    | 58.0         | 124.0          | 10.7             | 6.0                 | 3.9             |
|                        |                   | ♂   | 48        | 108       | 382       | 0.8               | 0.1                    | 41.0         | 67.0           | 10.0             | 5.7                 | 3.7             |
|                        |                   | ♂   | 36        | 87        | 198       | 0.8               | 0.1                    | 43.0         | 55.0           | 11.0             | 5.8                 | 3.8             |
|                        |                   | ♀   | 36        | 96        | 219       | 0.9               | 0.1                    | 52.0         | 77.0           | 11.2             | 5.8                 | 3.8             |
|                        | 29th Day          | ♂   | 57        | 84        | 300       | 0.7               | 0.3                    | 29.0         | 88.0           | 11.9             | 6.4                 | 4.1             |
|                        |                   | ♀   | 33        | 84        | 258       | 0.6               | 0.3                    | 23.0         | 84.0           | 12.1             | 6.6                 | 4.0             |
|                        |                   | ♂   | 51        | 84        | 222       | 0.6               | 0.2                    | 25.0         | 96.0           | 11.9             | 6.4                 | 4.1             |
|                        |                   | ♀   | 42        | 129       | 180       | 0.7               | 0.2                    | 40.0         | 104.0          | 11.8             | 5.9                 | 3.9             |
|                        |                   | ♂   | 39        | 102       | 159       | 0.8               | 0.2                    | 39.0         | 91             | 11.7             | 7.1                 | 4.3             |
|                        | 93rd Day          | ♂   | 39        | 99        | 165       | 0.5               | 0.2                    | 29.0         | 102            | 11.8             | 6.9                 | 4.4             |
|                        |                   | ♀   | 78        | 132       | 162       | 1.0               | 0.1                    | 35.0         | 84             | 9.1              | 6.7                 | 3.1             |
|                        |                   | ♀   | 72        | 156       | 162       | 1.0               | 0.2                    | 33.0         | 104            | 9.9              | 6.5                 | 3.3             |
|                        |                   | ♂   | 57        | 147       | 156       | 0.7               | 0.2                    | 37.0         | 114.0          | 11.0             | 7.4                 | 3.8             |
|                        |                   | ♀   | 54        | 129       | 198       | 0.9               | 0.2                    | 36.0         | 92.0           | 11.7             | 7.8                 | 4.1             |
|                        |                   | ♂   | 42        | 120       | 183       | 0.8               | 0.2                    | 37.0         | 106.0          | 11.0             | 7.6                 | 3.9             |
|                        |                   | ♀   | 63        | 138       | 123       | 0.8               | 0.2                    | 36.0         | 95.0           | 11.2             | 7.2                 | 3.7             |
|                        |                   | ♂   | 66        | 150       | 186       | 1.2               | 0.2                    | 38.0         | 81             | 9.3              | 6.4                 | 3.6             |
|                        |                   | ♀   | 72        | 156       | 144       | 1.2               | 0.2                    | 40.0         | 81             | 9.9              | 6.9                 | 3.5             |
|                        |                   | ♂   | 66        | 183       | 147       | 1.2               | 0.3                    | 40.0         | 65             | 10.1             | 6.6                 | 3.5             |
|                        |                   | ♀   | 30        | 93        | 135       | 0.8               | 0.3                    | 31.0         | 98.0           | 11.7             | 7.2                 | 4.2             |
|                        |                   | ♂   | 39        | 120       | 147       | 0.7               | 0.2                    | 34.0         | 82.0           | 11.8             | 7.3                 | 4.2             |
|                        |                   | ♀   | 69        | 186       | 126       | 0.7               | 0.2                    | 51.0         | 85.0           | 11.7             | 7.6                 | 4.5             |

(continued on next page)
Table 5 (continued)

| Group                        | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|------------------------------|-------------------|-----|-----------|-----------|-----------|-------------------|------------------------|--------------|----------------|----------------|----------------------|-----------------|
| Prophylactic Dose Intra-Nasal (PD-IN) | 15th Day          | ♂   | 51        | 114       | 288       | 0.6               | 0.1                    | 28.0         | 75.0           | 10.2           | 5.5                  | 3.8             |
|                              |                   | ♂   | 54        | 105       | 285       | 0.6               | 0.2                    | 33.0         | 77.0           | 10.6           | 5.7                  | 3.7             |
|                              |                   | ♂   | 57        | 90        | 303       | 0.7               | 0.2                    | 43.0         | 83.0           | 11.0           | 6.0                  | 3.7             |
|                              |                   | ♂   | 33        | 96        | 270       | 0.7               | 0.2                    | 37.0         | 60.0           | 10.6           | 5.4                  | 3.4             |
|                              |                   | ♂   | 51        | 117       | 219       | 0.7               | 0.2                    | 43.0         | 77.0           | 10.8           | 5.5                  | 3.8             |
|                              |                   | ♂   | 25        | 96        | 180       | 0.7               | 0.1                    | 35.0         | 76.0           | 10.8           | 5.9                  | 3.9             |
|                              | 29th Day          | ♂   | 66        | 114       | 285       | 0.7               | 0.3                    | 19.0         | 72.0           | 12.0           | 6.3                  | 4.0             |
|                              |                   | ♂   | 45        | 90        | 222       | 0.7               | 0.2                    | 25.0         | 81.0           | 11.8           | 6.6                  | 4.0             |
|                              |                   | ♂   | 54        | 105       | 195       | 0.7               | 0.3                    | 34.0         | 73.0           | 12.0           | 6.3                  | 4.1             |
|                              |                   | ♂   | 36        | 84        | 216       | 0.7               | 0.3                    | 32           | 97             | 12.2           | 6.5                  | 4.2             |
|                              |                   | ♂   | 48        | 138       | 174       | 0.7               | 0.3                    | 36           | 107            | 12.2           | 6.9                  | 4.3             |
|                              |                   | ♂   | 51        | 108       | 174       | 0.8               | 0.2                    | 34           | 80             | 12.4           | 6.9                  | 3.9             |
|                              | 93rd Day          | ♂   | 90        | 144       | 210       | 0.9               | 0.2                    | 34           | 106            | 11.0           | 7.6                  | 3.7             |
|                              |                   | ♂   | 87        | 153       | 186       | 0.8               | 0.2                    | 34           | 89             | 10.4           | 7.3                  | 3.5             |
|                              |                   | ♂   | 78        | 132       | 168       | 0.7               | 0.3                    | 33           | 94             | 10.4           | 6.7                  | 3.6             |
|                              |                   | ♂   | 75        | 114       | 195       | 0.8               | 0.2                    | 34           | 73             | 9.2             | 6.2                  | 3.2             |
|                              |                   | ♂   | 39        | 117       | 204       | 0.7               | 0.2                    | 34           | 82.0           | 11.1           | 6.9                  | 3.4             |
|                              |                   | ♂   | 81        | 258       | 201       | 0.7               | 0.3                    | 34           | 90.0           | 10.7           | 6.9                  | 3.8             |
|                              | 93rd Day          | ♂   | 66        | 150       | 156       | 1.2               | 0.2                    | 32           | 66             | 10.5           | 6.5                  | 3.7             |
|                              |                   | ♂   | 51        | 138       | 204       | 1.1               | 0.2                    | 44           | 69             | 10.1           | 6.9                  | 4.1             |
|                              |                   | ♂   | 66        | 123       | 162       | 0.9               | 0.2                    | 38           | 80             | 9.4            | 6.4                  | 3.8             |
|                              |                   | ♂   | 84        | 195       | 141       | 0.9               | 0.2                    | 21           | 72             | 10.1           | 6.9                  | 3.5             |

(continued on next page)
| Group                        | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|------------------------------|-------------------|-----|-----------|-----------|-----------|-------------------|------------------------|-------------|----------------|----------------|-------------------|-----------------|
| Prophylactic Dose Oral (PD-OR) | 15th Day          | ♂   | 39        | 138       | 354       | 0.6               | 0.2                    | 27.0        | 70.0           | 10.6            | 5.5               | 3.7             |
|                              |                   |     | 54        | 108       | 255       | 0.7               | 0.2                    | 34.0        | 60.0           | 10.7            | 5.4               | 3.7             |
|                              |                   | ♂   | 51        | 96        | 240       | 0.7               | 0.1                    | 42.0        | 73.0           | 10.4            | 6.1               | 3.6             |
|                              |                   | ♂   | 69        | 104       | 204       | 0.8               | 0.1                    | 42.0        | 87.0           | 10.7            | 5.9               | 3.9             |
|                              |                   | ♂   | 36        | 108       | 204       | 0.9               | 0.2                    | 38.0        | 93.0           | 10.4            | 5.9               | 3.8             |
|                              |                   | ♂   | 30        | 72        | 213       | 0.7               | 0.2                    | 30.0        | 77.0           | 10.2            | 6.3               | 3.6             |
|                              |                   | ♂   | 54        | 102       | 276       | 0.7               | 0.3                    | 26.0        | 85.0           | 11.9            | 6.6               | 4.1             |
|                              | 29th Day          | ♂   | 60        | 111       | 279       | 0.6               | 0.2                    | 20.0        | 99.0           | 12.4            | 6.3               | 4.1             |
|                              |                   |     | 60        | 117       | 306       | 0.7               | 0.3                    | 28.0        | 82.0           | 12.1            | 6.6               | 4.0             |
|                              |                   | ♂   | 48        | 96        | 192       | 0.6               | 0.2                    | 34.0        | 104.0          | 12.4            | 6.5               | 4.1             |
|                              |                   | ♂   | 54        | 84        | 216       | 0.7               | 0.1                    | 38.0        | 100.0          | 11.9            | 6.5               | 4.1             |
|                              |                   | ♂   | 45        | 99        | 180       | 0.7               | 0.2                    | 41.0        | 95.0           | 12.2            | 6.5               | 3.7             |
|                              | 93rd Day          | ♂   | 156       | 189       | 252       | 1.1               | 0.3                    | 34.0        | 71.0           | 11.1            | 7.4               | 3.5             |
|                              |                   | ♂   | 51        | 159       | 195       | 0.6               | 0.2                    | 35.0        | 86.0           | 11.2            | 5.9               | 3.7             |
|                              |                   | ♂   | 66        | 144       | 180       | 0.8               | 0.2                    | 32.0        | 74.0           | 12.0            | 7.5               | 3.9             |
|                              |                   | ♂   | 45        | 111       | 201       | 0.7               | 0.2                    | 34.0        | 76.0           | 11.5            | 6.9               | 3.8             |
|                              |                   | ♂   | 60        | 174       | 261       | 0.8               | 0.2                    | 41.0        | 107.0          | 11.8            | 7.1               | 3.9             |
|                              |                   | ♂   | 48        | 123       | 177       | 0.7               | 0.1                    | 41.0        | 88.0           | 10.8            | 6.6               | 3.7             |
|                              |                   | ♂   | 54        | 138       | 141       | 1.0               | 0.2                    | 37.0        | 76.0           | 10.1            | 6.1               | 3.5             |
|                              |                   | ♂   | 96        | 204       | 132       | 1.1               | 0.2                    | 37.0        | 93.0           | 10.0            | 6.3               | 3.5             |
|                              |                   | ♂   | 36        | 105       | 150       | 0.6               | 0.2                    | 48.0        | 64.0           | 11.8            | 7.3               | 4.3             |
|                              |                   | ♂   | 45        | 93        | 156       | 0.7               | 0.1                    | 38.0        | 83.0           | 10.9            | 7.1               | 3.8             |
|                              |                   | ♂   | 39        | 129       | 108       | 0.8               | 0.2                    | 39.0        | 80.0           | 12.0            | 7.6               | 4.3             |
|                              |                   | ♂   | 39        | 123       | 192       | 0.8               | 0.2                    | 43.0        | 55.0           | 12.1            | 7.0               | 3.8             |
| Group                        | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|-----------------------------|-------------------|-----|-----------|-----------|-----------|--------------------|------------------------|-------------|----------------|-----------------|------------------------|---------------|
| Average Dose Intra-Nasal (AD-IN) | 15th Day          | ♂   | 66        | 114       | 300       | 0.6                | 0.2                    | 32.0        | 71.0           | 10.7            | 5.8                    | 3.6            |
|                             |                   |     | 54        | 114       | 345       | 0.6                | 0.1                    | 31.0        | 75.0           | 10.4            | 5.3                    | 3.5            |
|                             |                   |     | 57        | 111       | 273       | 0.8                | 0.2                    | 26.0        | 60.0           | 11.1            | 5.8                    | 3.7            |
|                             |                   | ♂   | 39        | 99        | 216       | 0.7                | 0.2                    | 41.0        | 81.0           | 10.4            | 5.7                    | 3.6            |
|                             |                   |     | 30        | 105       | 201       | 0.8                | 0.2                    | 36.0        | 89.0           | 11.1            | 6.1                    | 3.9            |
|                             |                   | ♀   | 54        | 144       | 181       | 0.7                | 0.2                    | 38.0        | 102.0          | 10.4            | 5.4                    | 3.4            |
|                             | 29th Day           | ♂   | 48        | 105       | 258       | 0.6                | 0.2                    | 24.0        | 77.0           | 11.7            | 6.7                    | 4.0            |
|                             |                   |     | 51        | 84        | 219       | 0.5                | 0.2                    | 33.0        | 94.0           | 12.0            | 6.3                    | 4.1            |
|                             |                   | ♂   | 39        | 99        | 231       | 0.8                | 0.2                    | 43.0        | 73.0           | 12.4            | 6.8                    | 4.4            |
|                             |                   |     | 45        | 105       | 210       | 0.7                | 0.2                    | 46.0        | 91.0           | 12.2            | 6.4                    | 3.8            |
|                             |                   | ♀   | 48        | 108       | 183       | 0.9                | 0.3                    | 53.0        | 74.0           | 12.6            | 6.9                    | 3.9            |
|                             |                   |     | 42        | 123       | 219       | 0.8                | 0.3                    | 47.0        | 71.0           | 13.2            | 6.6                    | 3.9            |
|                             | 93rd Day           | ♂   | 150       | 162       | 234       | 1.0                | 0.3                    | 37.0        | 86.0           | 9.4             | 7.5                    | 3.3            |
|                             |                   |     | 45        | 129       | 156       | 0.8                | 0.3                    | 31.0        | 117.0          | 10.8            | 7.3                    | 3.9            |
|                             |                   | ♀   | 84        | 240       | 207       | 0.7                | 0.3                    | 46.0        | 87.0           | 11.4            | 7.2                    | 3.7            |
|                             |                   |     | 87        | 135       | 165       | 0.7                | 0.1                    | 40.0        | 69.0           | 11.4            | 7.1                    | 3.8            |
|                             |                   |     | 90        | 246       | 201       | 0.7                | 0.2                    | 42.0        | 72.0           | 11.3            | 7.1                    | 3.8            |
|                             |                   | ♀   | 69        | 168       | 207       | 0.6                | 0.2                    | 34.0        | 84.0           | 11.4            | 6.7                    | 3.9            |
|                             |                   |     | 66        | 120       | 189       | 1.1                | 0.2                    | 33.0        | 88.0           | 10.4            | 7.0                    | 3.1            |
|                             |                   |     | 54        | 132       | 162       | 1.0                | 0.5                    | 40.0        | 85.0           | 9.6             | 6.7                    | 3.8            |
|                             |                   | ♀   | 81        | 177       | 150       | 1.2                | 0.3                    | 36.0        | 126.0          | 10.1            | 6.7                    | 3.4            |
|                             |                   |     | 111       | 198       | 135       | 0.7                | 0.1                    | 46.0        | 89.0           | 11.8            | 6.7                    | 3.8            |
|                             |                   |     | 39        | 105       | 165       | 0.7                | 0.2                    | 33.0        | 81.0           | 11.8            | 7.4                    | 3.9            |
|                             |                   |     | 36        | 99        | 156       | 0.6                | 0.2                    | 33.0        | 98.0           | 11.1            | 7.1                    | 4.1            |
Table 6
Biochemical profile of rabbits used for subchronic testing of rSt.HPV expressing HPV 16 and 18 L1 proteins.

| Group          | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|----------------|-------------------|-----|-----------|-----------|-----------|--------------------|------------------------|--------------|-----------------|-----------------|----------------------|-----------------|
| Vehicle Control | 14th Day          | ♂   | 36.00     | 21.00     | 243.00    | 1.10               | 0.10                   | 47.00        | 145.00          | 13.90           | 7.30                 | 3.40            |
|                |                   |     | 87.00     | 45.00     | 369.00    | 1.50               | 0.20                   | 36.00        | 112.00          | 13.90           | 7.10                 | 3.50            |
|                |                   |     | 60.00     | 39.00     | 129.00    | 1.50               | 0.30                   | 46.00        | 144.00          | 14.30           | 8.10                 | 3.80            |
|                |                   | ♂   | 27.00     | 15.00     | 345.00    | 1.00               | 0.40                   | 37.00        | 119.00          | 12.80           | 8.90                 | 2.80            |
|                |                   |     | 30.00     | 18.00     | 186.00    | 1.30               | 0.30                   | 42.00        | 104.00          | 13.90           | 6.80                 | 3.00            |
|                | 28th Day          | ♂   | 63.00     | 36.00     | 104.00    | 1.20               | 0.20                   | 35.00        | 180.00          | 16.60           | 8.40                 | 3.50            |
|                |                   |     | 69.00     | 24.00     | 273.00    | 1.50               | 0.20                   | 40.00        | 150.00          | 15.30           | 7.10                 | 3.40            |
|                |                   | ♂   | 54.00     | 15.00     | 276.00    | 1.60               | 0.10                   | 56.00        | 138.00          | 16.30           | 6.70                 | 3.50            |
|                |                   |     | 51.00     | 24.00     | 180.00    | 1.80               | 0.30                   | 60.00        | 119.00          | 16.00           | 6.70                 | 3.40            |
|                |                   | ♂   | 39.00     | 15.00     | 225.00    | 1.40               | 0.20                   | 58.00        | 108.00          | 16.80           | 6.90                 | 3.50            |
|                | 93rd Day          | ♂   | 12.00     | 84.00     | 69.00     | 1.30               | 0.20                   | 34.00        | 134.00          | 12.90           | 6.50                 | 3.40            |
|                |                   |     | 36.00     | 27.00     | 78.00     | 1.20               | 0.30                   | 72.00        | 126.00          | 14.40           | 7.40                 | 3.10            |
|                |                   |     | 120.00    | 167.00    | 69.00     | 1.50               | 0.20                   | 30.00        | 111.00          | 9.70            | 6.30                 | 3.10            |
|                |                   | ♂   | 48.00     | 24.00     | 93.00     | 1.20               | 0.10                   | 35.00        | 96.00           | 11.00           | 6.10                 | 3.20            |
|                |                   |     | 39.00     | 72.00     | 60.00     | 1.60               | 0.20                   | 41.00        | 110.00          | 14.30           | 7.40                 | 3.30            |
|                |                   | ♂   | 66.00     | 103.00    | 87.00     | 1.60               | 0.30                   | 31.00        | 145.00          | 12.80           | 7.10                 | 3.00            |
|                |                   |     | 27.00     | 45.00     | 99.00     | 1.00               | 0.30                   | 41.00        | 124.00          | 14.80           | 7.10                 | 3.40            |
|                |                   |     | 30.00     | 39.00     | 72.00     | 1.50               | 0.30                   | 32.00        | 111.00          | 13.10           | 6.60                 | 2.90            |
|                |                   | ♂   | 27.00     | 26.00     | 84.00     | 2.00               | 0.30                   | 37.00        | 135.00          | 16.30           | 6.70                 | 3.70            |

(continued on next page)
Table 6 (continued)

| Group                      | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|----------------------------|-------------------|-----|-----------|-----------|-----------|-------------------|--------------------------|--------------|----------------|-------------------|---------------------|---------------|
| Experimental Control (Intranasal) | 14th Day          | ♂   | 27.00     | 30.00     | 150.00    | 0.90              | 0.30                     | 34.00        | 114.00         | 14.00             | 7.30                | 3.40          |
|                             |                   | ♀   | 57.00     | 45.00     | 324.00    | 1.50              | 0.20                     | 39.00        | 139.00         | 16.80             | 8.20                | 3.60          |
|                             | 28th Day          | ♂   | 75.00     | 36.00     | 408.00    | 1.70              | 0.20                     | 53.00        | 123.00         | 16.70             | 7.10                | 3.70          |
|                             |                   | ♀   | 75.00     | 24.00     | 231.00    | 1.40              | 0.20                     | 52.00        | 126.00         | 15.50             | 7.60                | 3.70          |
|                             | 93rd Day          | ♂   | 36.00     | 79.00     | 102.00    | 1.80              | 0.20                     | 46.00        | 99.00          | 12.10             | 6.20                | 3.00          |
|                             |                   | ♀   | 51.00     | 21.00     | 90.00     | 1.20              | 0.20                     | 33.00        | 106.00         | 13.30             | 6.20                | 3.20          |
|                             |                   |      | 87.00     | 99.00     | 96.00     | 1.60              | 0.30                     | 42.00        | 98.00          | 10.30             | 5.10                | 2.60          |
|                             |                   |      | 159.00    | 78.00     | 120.00    | 1.40              | 0.20                     | 36.00        | 100.00         | 11.50             | 7.70                | 2.60          |
|                             |                   |      | 57.00     | 15.00     | 84.00     | 1.70              | 0.20                     | 51.00        | 117.00         | 15.20             | 6.00                | 3.50          |
|                             |                   |      | 91.00     | 102.00    | 30.00     | 1.30              | 0.20                     | 65.00        | 114.00         | 13.00             | 8.10                | 2.70          |
|                             |                   | ♂   | 35.00     | 27.00     | 126.00    | 1.30              | 0.30                     | 44.00        | 89.00          | 11.50             | 5.70                | 2.80          |
|                             |                   | ♀   | 105.00    | 51.00     | 105.00    | 1.60              | 0.30                     | 38.00        | 97.00          | 11.60             | 6.00                | 2.70          |
|                             |                   |      | 42.00     | 24.00     | 180.00    | 1.60              | 0.30                     | 40.00        | 97.00          | 10.80             | 4.90                | 2.60          |
|                             |                   |      | 48.00     | 30.00     | 96.00     | 2.40              | 0.30                     | 43.00        | 131.00         | 16.90             | 7.10                | 3.60          |

(continued on next page)
| Group                  | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|-----------------------|-------------------|-----|-----------|-----------|-----------|-------------------|------------------------|--------------|-----------------|------------------|----------------------|-----------------|
| **Experimental**      |                   |     |           |           |           |                   |                        |              |                 |                  |                      |                 |
| Control (Oral)        | 14th Day          | ♂   | 105.00    | 69.00     | 165.00    | 1.20              | 0.20                   | 26.00        | 110.00          | 12.30            | 7.10                 | 3.20            |
|                       |                   |     | 27.00     | 36.00     | 273.00    | 1.60              | 0.30                   | 38.00        | 118.00          | 15.20            | 7.00                 | 3.70            |
|                       |                   | ♂   | 39.00     | 30.00     | 186.00    | 1.60              | 0.30                   | 50.00        | 118.00          | 14.30            | 7.20                 | 3.20            |
|                       |                   |     | 33.00     | 29.00     | 189.00    | 1.40              | 0.20                   | 47.00        | 134.00          | 14.40            | 6.70                 | 3.10            |
|                       | 28th Day          | ♂   | 63.00     | 24.00     | 204.00    | 1.50              | 0.20                   | 51.00        | 129.00          | 15.30            | 6.70                 | 3.50            |
|                       |                   |     | 24.00     | 15.00     | 435.00    | 1.10              | 0.10                   | 47.00        | 129.00          | 14.00            | 7.90                 | 3.50            |
|                       |                   | ♂   | 27.00     | 12.00     | 303.00    | 1.40              | 0.30                   | 42.00        | 108.00          | 15.50            | 5.90                 | 3.30            |
|                       |                   |     | 39.00     | 18.00     | 336.00    | 1.10              | 0.20                   | 36.00        | 114.00          | 15.20            | 6.10                 | 3.10            |
|                       |                   | ♂   | 48.00     | 9.00      | 207.00    | 1.30              | 0.30                   | 48.00        | 111.00          | 15.00            | 6.80                 | 3.50            |
|                       | 93rd Day          | ♂   | 84.00     | 81.00     | 123.00    | 2.00              | 0.30                   | 34.00        | 182.00          | 16.60            | 7.30                 | 3.80            |
|                       |                   |     | 48.00     | 84.00     | 93.00     | 1.50              | 0.30                   | 60.00        | 101.00          | 14.80            | 7.70                 | 3.70            |
|                       |                   | ♂   | 90.00     | 105.00    | 165.00    | 1.10              | 0.20                   | 60.00        | 111.00          | 13.30            | 9.10                 | 2.90            |
|                       |                   |     | 30.00     | 84.00     | 21.00     | 0.90              | 0.10                   | 33.00        | 125.00          | 13.40            | 7.40                 | 3.10            |
|                       |                   | ♂   | 42.00     | 141.00    | 87.00     | 1.70              | 0.20                   | 45.00        | 219.00          | 14.50            | 7.10                 | 3.50            |
|                       |                   |     | 18.00     | 87.00     | 87.00     | 1.90              | 0.10                   | 52.00        | 119.00          | 14.00            | 6.70                 | 3.10            |
|                       |                   | ♂   | 51.00     | 51.00     | 144.00    | 1.40              | 0.20                   | 36.00        | 113.00          | 13.20            | 6.00                 | 2.90            |
|                       |                   |     | 60.00     | 42.00     | 198.00    | 1.30              | 0.20                   | 32.00        | 117.00          | 13.10            | 5.80                 | 2.90            |
|                       |                   | ♂   | 13.00     | 15.00     | 105.00    | 1.70              | 0.20                   | 40.00        | 125.00          | 16.50            | 7.90                 | 3.80            |
|                       |                   |     | 18.00     | 27.00     | 96.00     | 1.60              | 0.30                   | 38.00        | 103.00          | 9.90             | 5.40                 | 2.50            |

Table 6 (continued)
Table 6 (continued)

| Group                              | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|------------------------------------|-------------------|-----|-----------|-----------|-----------|--------------------|------------------------|--------------|-----------------|------------------|---------------------|---------------|
|                                    |                   | ♂   | 18.00     | 48.00     | 174.00    | 1.40               | 0.20                   | 35.00        | 108.00          | 13.80             | 7.30                | 3.30          |
|                                    |                   |     | 42.00     | 18.00     | 132.00    | 1.00               | 0.30                   | 112.00       | 147.00          | 12.90             | 8.60                | 3.10          |
|                                    |                   |     | 60.00     | 27.00     | 216.00    | 1.80               | 0.40                   | 53.00        | 139.00          | 14.20             | 7.30                | 3.60          |
|                                    |                   |     | 30.00     | 24.00     | 117.00    | 1.20               | 0.20                   | 59.00        | 118.00          | 15.30             | 9.20                | 3.30          |
|                                    |                   |     | 33.00     | 29.00     | 192.00    | 1.30               | 0.20                   | 43.00        | 122.00          | 13.10             | 7.30                | 3.00          |
| Prophylactic Dose (PD) Intra-Nasal | 14th Day          | ♂   | 18.00     | 48.00     | 174.00    | 1.40               | 0.20                   | 35.00        | 108.00          | 13.80             | 7.30                | 3.30          |
|                                    |                   |     | 42.00     | 18.00     | 132.00    | 1.00               | 0.30                   | 112.00       | 147.00          | 12.90             | 8.60                | 3.10          |
|                                    |                   |     | 60.00     | 27.00     | 216.00    | 1.80               | 0.40                   | 53.00        | 139.00          | 14.20             | 7.30                | 3.60          |
|                                    |                   | ♂   | 45.00     | 20.00     | 375.00    | 1.40               | 0.20                   | 45.00        | 115.00          | 15.30             | 8.30                | 3.60          |
|                                    |                   |     | 72.00     | 30.00     | 198.00    | 1.40               | 0.10                   | 45.00        | 137.00          | 16.10             | 7.20                | 3.70          |
|                                    |                   | ♂   | 24.00     | 18.00     | 204.00    | 1.30               | 0.40                   | 33.00        | 94.00           | 16.50             | 7.20                | 3.60          |
|                                    |                   |     | 42.00     | 18.00     | 231.00    | 1.60               | 0.20                   | 39.00        | 101.00          | 15.00             | 6.80                | 3.40          |
|                                    |                   | ♂   | 36.00     | 15.00     | 168.00    | 1.50               | 0.20                   | 44.00        | 109.00          | 15.10             | 5.90                | 3.30          |
|                                    |                   |     | 33.00     | 12.00     | 78.00     | 1.30               | 0.10                   | 32.00        | 104.00          | 14.00             | 6.40                | 3.00          |
|                                    |                   |     | 63.00     | 33.00     | 105.00    | 1.60               | 0.20                   | 27.00        | 116.00          | 15.50             | 7.60                | 3.20          |
|                                    |                   |     | 64.00     | 24.00     | 102.00    | 1.30               | 0.30                   | 26.00        | 127.00          | 16.20             | 7.40                | 3.80          |
|                                    |                   |     | 84.00     | 27.00     | 141.00    | 1.60               | 0.30                   | 32.00        | 95.00           | 11.40             | 5.40                | 2.60          |
|                                    |                   |     | 42.00     | 78.00     | 72.00     | 1.10               | 0.30                   | 43.00        | 114.00          | 14.20             | 7.70                | 3.30          |
|                                    |                   | ♂   | 51.00     | 141.00    | 42.00     | 1.40               | 0.30                   | 69.00        | 125.00          | 12.40             | 8.20                | 3.00          |
|                                    |                   |     | 15.00     | 78.00     | 60.00     | 1.70               | 0.20                   | 42.00        | 115.00          | 14.40             | 6.90                | 3.40          |
|                                    |                   | ♂   | 30.00     | 12.00     | 107.00    | 1.60               | 0.30                   | 40.00        | 117.00          | 15.80             | 6.30                | 3.40          |
|                                    |                   |     | 99.00     | 48.00     | 258.00    | 1.60               | 0.40                   | 42.00        | 89.00           | 10.80             | 6.10                | 2.50          |

(continued on next page)
Table 6 (continued)

| Group                              | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|------------------------------------|-------------------|-----|-----------|-----------|-----------|--------------------|------------------------|--------------|-----------------|------------------|---------------------|-----------------|
| **Prophylactic Dose (PD) Oral**    |                   |     |           |           |           |                    |                        |              |                 |                  |                     |                 |
| 14th Day                           | ♂                 | 33.00 | 27.00     | 378.00    | 0.20      | 1.30               | 45.00                  | 137.00       | 16.40           | 8.50             | 3.60                |                 |
|                                   | 27.00             | 21.00 | 252.00    | 1.40      | 0.20      | 1.20               | 54.00                  | 101.00       | 13.60           | 6.20             | 3.50                |                 |
|                                   | 27.00             | 27.00 | 255.00    | 1.50      | 0.20      | 1.20               | 34.00                  | 129.00       | 16.50           | 9.60             | 3.80                |                 |
|                                   | ♂                 | 42.00 | 29.00     | 219.00    | 0.30      | 1.40               | 40.00                  | 114.00       | 14.90           | 7.90             | 3.30                |                 |
|                                   | 33.00             | 16.00 | 321.00    | 0.20      | 0.20      | 1.40               | 53.00                  | 131.00       | 13.20           | 6.80             | 2.80                |                 |
| 28th Day                           | ♂                 | 39.00 | 18.00     | 183.00    | 0.20      | 1.10               | 45.00                  | 121.00       | 15.90           | 7.30             | 3.60                |                 |
|                                   | 21.00             | 21.00 | 195.00    | 1.20      | 0.10      | 1.20               | 29.00                  | 132.00       | 16.20           | 7.80             | 3.60                |                 |
|                                   | ♂                 | 69.00 | 9.00      | 297.00    | 0.30      | 1.10               | 38.00                  | 117.00       | 15.70           | 6.60             | 3.30                |                 |
|                                   | 57.00             | 15.00 | 216.00    | 0.20      | 0.20      | 1.30               | 39.00                  | 118.00       | 15.10           | 5.60             | 3.20                |                 |
|                                   | 36.00             | 12.00 | 210.00    | 0.10      | 0.10      | 1.50               | 46.00                  | 108.00       | 15.10           | 5.70             | 3.00                |                 |
| 93rd Day                           | ♂                 | 81.00 | 24.00     | 78.00     | 0.30      | 1.40               | 37.00                  | 107.00       | 10.90           | 5.20             | 2.70                |                 |
|                                   | 48.00             | 27.00 | 114.00    | 0.30      | 0.30      | 1.20               | 45.00                  | 99.00        | 10.00           | 5.20             | 2.70                |                 |
|                                   | 84.00             | 60.00 | 96.00     | 0.30      | 0.30      | 1.90               | 39.00                  | 116.00       | 14.80           | 6.30             | 3.50                |                 |
|                                   | 78.00             | 108.00| 297.00    | 0.20      | 0.20      | 1.80               | 32.00                  | 115.00       | 12.50           | 6.20             | 2.90                |                 |
|                                   | 33.00             | 30.00 | 48.00     | 0.20      | 0.20      | 1.50               | 34.00                  | 107.00       | 13.50           | 6.80             | 2.90                |                 |
|                                   | ♂                 | 30.00 | 69.00     | 39.00     | 0.30      | 1.10               | 25.00                  | 114.00       | 12.30           | 6.90             | 2.60                |                 |
|                                   | 18.00             | 15.00 | 156.00    | 0.20      | 0.20      | 1.70               | 40.00                  | 125.00       | 15.40           | 6.40             | 3.40                |                 |
|                                   | 24.00             | 29.00 | 102.00    | 0.20      | 0.20      | 1.90               | 64.00                  | 143.00       | 15.30           | 6.90             | 3.60                |                 |
|                                   | 36.00             | 81.00 | 45.00     | 1.10      | 0.30      | 1.10               | 41.00                  | 114.00       | 13.80           | 7.60             | 3.10                |                 |
|                                   | 21.00             | 15.00 | 108.00    | 0.30      | 0.30      | 1.40               | 35.00                  | 98.00        | 11.00           | 5.20             | 2.60                |                 |

(continued on next page)
Table 6 (continued)

| Group                        | Euthanization Day | Sex | ALT (U/L) | AST (U/L) | ALP (U/L) | Creatinine (mg/dL) | Total Bilirubin (mg/dL) | Urea (mg/dL) | Glucose (mg/dL) | Calcium (mg/dL) | Total Protein (g/dL) | Albumin (g/dL) |
|------------------------------|-------------------|-----|-----------|-----------|-----------|--------------------|------------------------|--------------|---------------|-----------------|-------------------|-----------------|
| Average Dose (AD) Intra-Nasal | 14th Day          | ♂   | 60.00     | 30.00     | 291.00    | 1.50               | 0.30                   | 48.00        | 123.00        | 14.70           | 7.60              | 3.20            |
|                              |                   | ♂   | 33.00     | 16.00     | 138.00    | 0.70               | 0.40                   | 103.00       | 109.00        | 13.00           | 8.30              | 2.50            |
|                              |                   | ♂   | 15.00     | 23.00     | 195.00    | 1.10               | 0.20                   | 39.00        | 128.00        | 13.80           | 6.30              | 2.90            |
|                              |                   | ♂   | 39.00     | 14.00     | 126.00    | 1.00               | 0.30                   | 68.00        | 102.00        | 14.30           | 9.10              | 3.20            |
|                              |                   | ♂   | 27.00     | 14.00     | 168.00    | 1.10               | 0.20                   | 52.00        | 134.00        | 14.30           | 7.50              | 3.20            |
|                              |                   | ♀   | 39.00     | 14.00     | 126.00    | 1.00               | 0.30                   | 68.00        | 102.00        | 14.30           | 9.10              | 3.20            |
|                              |                   | ♀   | 27.00     | 14.00     | 168.00    | 1.10               | 0.20                   | 52.00        | 134.00        | 14.30           | 7.50              | 3.20            |
|                              | 28th Day          | ♂   | 54.00     | 33.00     | 264.00    | 1.60               | 0.10                   | 46.00        | 116.00        | 15.60           | 7.50              | 3.80            |
|                              |                   | ♂   | 51.00     | 21.00     | 207.00    | 1.30               | 0.20                   | 60.00        | 128.00        | 15.00           | 7.30              | 3.60            |
|                              |                   | ♂   | 102.00    | 30.00     | 405.00    | 1.30               | 0.10                   | 33.00        | 105.00        | 14.90           | 5.60              | 3.10            |
|                              |                   | ♂   | 36.00     | 12.00     | 246.00    | 1.40               | 0.20                   | 41.00        | 107.00        | 15.00           | 6.30              | 3.20            |
|                              |                   | ♂   | 36.00     | 15.00     | 204.00    | 1.30               | 0.30                   | 39.00        | 115.00        | 15.80           | 6.60              | 3.40            |
|                              |                   | ♀   | 51.00     | 101.00    | 54.00     | 1.40               | 0.20                   | 42.00        | 110.00        | 13.70           | 8.90              | 3.10            |
|                              |                   | ♀   | 12.00     | 78.00     | 78.00     | 1.90               | 0.20                   | 59.00        | 114.00        | 12.60           | 7.90              | 3.10            |
|                              |                   | ♀   | 69.00     | 39.00     | 210.00    | 1.50               | 0.30                   | 33.00        | 111.00        | 16.40           | 7.20              | 3.70            |
|                              |                   | ♀   | 60.00     | 21.00     | 138.00    | 1.50               | 0.30                   | 33.00        | 109.00        | 16.00           | 6.30              | 3.60            |
|                              |                   | ♀   | 42.00     | 21.00     | 108.00    | 1.40               | 0.20                   | 30.00        | 109.00        | 11.40           | 5.30              | 2.60            |
|                              |                   | ♀   | 102.00    | 49.00     | 144.00    | 1.10               | 0.40                   | 32.00        | 96.00         | 13.20           | 8.00              | 3.10            |
|                              |                   | ♀   | 66.00     | 36.00     | 114.00    | 1.50               | 0.50                   | 41.00        | 119.00        | 14.30           | 6.90              | 3.40            |
|                              |                   | ♀   | 48.00     | 21.00     | 72.00     | 1.80               | 0.20                   | 40.00        | 182.00        | 15.60           | 6.30              | 3.40            |
|                              |                   | ♀   | 30.00     | 6.00      | 81.00     | 1.60               | 0.30                   | 46.00        | 130.00        | 11.20           | 6.40              | 2.80            |
|                              |                   | ♀   | 78.00     | 48.00     | 309.00    | 1.70               | 0.40                   | 45.00        | 113.00        | 11.00           | 5.40              | 2.70            |
### Table 7.1
Organ Weights of rats Euthanized on 15th Day of Post-Exposure of recombinant HPV vaccine.

| Group                  | Time Point | Sex | Brain (g) | Heart (g) | Kidney L & R (g) | Liver (g) | Lungs L & R (g) | Spleen (g) | Testis L & R (g) |
|------------------------|------------|-----|-----------|-----------|-------------------|-----------|-----------------|------------|-----------------|
| Vehicle Control        | 15th Day   | ♂   | 1.7       | 0.9       | 1.4               | 5.6       | 1.3             | 0.4        | 2.1             |
|                        |            |     | 1.8       | 0.9       | 1.6               | 6.4       | 1.1             | 0.2        | 3.7             |
|                        |            | ♂   | 1.6       | 0.8       | 1.5               | 5.9       | 1.5             | 0.3        | 2.5             |
|                        |            | ♂   | 1.8       | 0.8       | 1.5               | 4.9       | 1.2             | 0.4        | NA              |
|                        |            | ♂   | 1.5       | 0.8       | 1.5               | 5.4       | 1.5             | 0.3        | NA              |
|                        |            | ♂   | 1.7       | 0.7       | 1.6               | 5.5       | 1.3             | 0.4        | NA              |
| Experimental Control   | IN         | 15th Day | ♂   | 1.5       | 1.0               | 1.5       | 5.5             | 1.1        | 3.4             |
|                        |            |     | 1.6       | 1.1       | 1.9               | 7.2       | 1.2             | 0.3        | 3.7             |
|                        |            | ♂   | 1.5       | 0.7       | 1.7               | 5.3       | 1.8             | 0.4        | 3.8             |
|                        |            | ♂   | 1.7       | 0.7       | 1.4               | 4.9       | 1.4             | 0.4        | NA              |
|                        |            | ♂   | 1.7       | 0.7       | 1.4               | 4.6       | 1.1             | 0.4        | NA              |
|                        |            | ♂   | 1.7       | 0.8       | 1.6               | 5.0       | 1.1             | 0.4        | NA              |
| Oral                   | 15th Day   | ♂   | 1.7       | 0.9       | 1.9               | 6.1       | 1.6             | 0.4        | 3.3             |
|                        |            |     | 1.6       | 0.7       | 1.5               | 5.9       | 1.3             | 0.3        | 3.1             |
|                        |            | ♂   | 1.8       | 0.8       | 1.5               | 4.9       | 1.2             | 0.3        | 3.7             |
|                        |            | ♂   | 1.7       | 0.8       | 1.5               | 5.5       | 1.2             | 0.3        | NA              |
|                        |            | ♂   | 1.6       | 0.9       | 1.5               | 6.1       | 1.5             | 0.4        | NA              |
| Prophylactic Dose (PD) | IN         | 15th Day | ♂   | 1.4       | 0.9               | 1.6       | 6.2             | 1.1        | 4.4             |
|                        |            |     | 1.8       | 1.0       | 1.6               | 7.0       | 1.5             | 0.5        | 2.6             |
|                        |            | ♂   | 1.7       | 1.1       | 1.8               | 6.1       | 1.4             | 0.4        | 4.6             |
|                        |            | ♂   | 1.5       | 0.9       | 1.6               | 4.7       | 1.5             | 0.6        | NA              |
|                        |            | ♂   | 1.9       | 0.8       | 1.4               | 5.4       | 1.3             | 0.4        | NA              |
|                        |            | ♂   | 1.5       | 1.1       | 1.8               | 5.9       | 1.4             | 0.4        | NA              |
| Oral                   | 15th Day   | ♂   | 1.8       | 1.1       | 1.8               | 6.8       | 1.2             | 0.5        | 3.6             |
|                        |            |     | 1.8       | 1.0       | 1.9               | 6.3       | 1.4             | 0.3        | 5.4             |
|                        |            | ♂   | 1.8       | 1.1       | 2.2               | 6.5       | 2.0             | 0.4        | 4.4             |
|                        |            | ♂   | 1.6       | 1.0       | 1.9               | 5.7       | 1.4             | 0.4        | NA              |
|                        |            | ♂   | 1.8       | 1.4       | 2.1               | 6.6       | 1.5             | 0.5        | NA              |
|                        |            | ♂   | 1.8       | 0.8       | 1.8               | 6.0       | 1.4             | 0.4        | NA              |
| Average Dose (IN)      | 15th Day   | ♂   | 1.6       | 1.1       | 1.7               | 5.5       | 1.8             | 0.4        | 4.1             |
|                        |            |     | 1.8       | 1.1       | 1.9               | 6.4       | 1.4             | 0.4        | 3.8             |
|                        |            | ♂   | 1.9       | 1.1       | 2.4               | 8.2       | 1.7             | 0.5        | 5.8             |
|                        |            | ♂   | 1.7       | 1.1       | 1.8               | 5.3       | 1.7             | 0.5        | NA              |
|                        |            | ♂   | 1.7       | 1.1       | 1.8               | 5.8       | 1.4             | 0.5        | NA              |
|                        |            | ♂   | 1.8       | 0.6       | 1.5               | 4.5       | 1.0             | 0.4        | NA              |

L & R: Left and Right Kidneys, Lungs and Testis; NA: Not Applicable.

The Table 9 data consist of bone marrow micronucleus levels in rats administered with rSt.HPV expressing HPV 16 and 18 L1 proteins as part of sub-chronic testing of vaccine. Similarly, the Table 10 comprised of data of bone marrow micronucleus of rabbits used for sub-chronic testing of rSt.HPV vaccine.

The immune response in terms of specific IgG levels against HPV 16 L1 and 18 L1 proteins were given in Table 11. Similarly, the allergenicity of rSt.HPV expressing HPV 16 and 18 L1 proteins, if any assessed in terms of specific IgE levels against HPV 16 L1 and 18 L1 proteins were given in Table 12.

### 2. Experimental Design, Materials and Methods

The nonclinical efficacy and safety/toxicology of recombinant *S. typhi* Ty21a expressing HPV 16 and 18 L1 proteins was generated previously [1]. Selection of animals species, strain, sex, age and weight of animals were illustrated in the research article published in vaccine journal [1]. The animals were obtained from National Centre for Laboratory Animals Sciences (ICMR-NIN), Hyderabad. Data of current article collected from rats and rabbits administered with attenuated
Table 7.2
Organ Weights of rats Euthanized on 29th Day of Post-Exposure of recombinant HPV vaccine.

| Group              | Time Point | Sex | Brain (g) | Heart (g) | Kidney (L & R) (g) | Liver (g) | Lungs (L & R) (g) | Spleen (g) | Testis (L & R) (g) |
|--------------------|------------|-----|-----------|-----------|--------------------|-----------|------------------|------------|-------------------|
| Vehicle Control    | 29th Day   | ♂   | 1.8       | 0.9       | 1.6                | 6.6       | 1.8              | 0.4        | 3.8               |
|                    |            | ♂   | 1.5       | 1.2       | 1.8                | 7.2       | 1.6              | 0.5        | 2.8               |
|                    |            | ♂   | 1.8       | 1.4       | 2.2                | 7.5       | 3.0              | 0.6        | 4.8               |
|                    |            | ♂   | 1.9       | 0.8       | 1.6                | 5.9       | 1.9              | 0.4        | NA                |
|                    |            | ♂   | 1.7       | 0.9       | 1.5                | 5.7       | 1.6              | 0.5        | NA                |
|                    |            | ♂   | 1.4       | 0.6       | 1.4                | 4.5       | 1.6              | 0.3        | NA                |
| Experimental       | IN         | 29th Day | ♂   | 4.3       | 1.0               | 1.6       | 5.3              | 1.2        | 0.2               |
| Control            |            | ♂   | 1.9       | 0.8       | 1.7                | 6.9       | 1.3              | 0.4        | 2.9               |
|                    |            | ♂   | 1.8       | 0.9       | 1.6                | 6.3       | 1.6              | 0.2        | 3.2               |
|                    |            | ♂   | 1.7       | 1.0       | 1.6                | 5.4       | 3.0              | 0.3        | NA                |
|                    |            | ♂   | 1.8       | 0.7       | 1.6                | 4.9       | 1.3              | 0.2        | NA                |
|                    |            | ♂   | 1.7       | 0.9       | 2.0                | 6.7       | 1.4              | 0.5        | NA                |
| Oral               | IN         | 29th Day | ♂   | 1.4       | 1.1               | 1.8       | 7.1              | 2.6        | 0.4               |
|                    |            | ♂   | 1.8       | 1.2       | 1.9                | 6.2       | 1.9              | 0.6        | 2.9               |
|                    |            | ♂   | 1.6       | 1.2       | 2.1                | 6.8       | 1.4              | 0.5        | 4.4               |
|                    |            | ♂   | 1.8       | 0.9       | 1.6                | 4.9       | 1.2              | 0.3        | NA                |
|                    |            | ♂   | 1.4       | 0.8       | 1.7                | 5.1       | 1.7              | 1.3        | NA                |
|                    |            | ♂   | 1.9       | 1.1       | 1.9                | 6.9       | 1.4              | 0.4        | NA                |
| Prophylactic       | IN         | 29th Day | ♂   | 1.6       | 1.1               | 2.2       | 5.8              | 1.8        | 1.5               |
| Dose (PD)          |            | ♂   | 1.9       | 1.1       | 1.9                | 8.1       | 1.7              | 0.6        | 5.5               |
|                    |            | ♂   | 1.8       | 1.3       | 2.5                | 9.3       | 1.8              | 0.5        | 4.2               |
|                    |            | ♂   | 1.7       | 0.8       | 1.5                | 5.4       | 1.3              | 0.4        | NA                |
|                    |            | ♂   | 1.5       | 1.0       | 1.6                | 5.5       | 1.7              | 0.3        | NA                |
|                    |            | ♂   | 1.7       | 0.8       | 1.8                | 5.2       | 1.7              | 0.4        | NA                |
| Oral               | IN         | 29th Day | ♂   | 1.8       | 0.9               | 1.6       | 6.4              | 1.1        | 0.3               |
|                    |            | ♂   | 1.8       | 1.0       | 1.6                | 6.5       | 1.4              | 0.4        | 3.5               |
|                    |            | ♂   | 1.7       | 1.2       | 1.7                | 6.8       | 1.7              | 0.4        | 5.1               |
|                    |            | ♂   | 1.4       | 0.8       | 1.7                | 6.4       | 1.4              | 0.4        | NA                |
|                    |            | ♂   | 1.4       | 1.0       | 1.8                | 6.6       | 1.7              | 0.5        | NA                |
|                    |            | ♂   | 1.8       | 1.0       | 1.6                | 6.6       | 1.4              | 0.4        | NA                |
| Average Dose (IN)  | 29th Day   | ♂   | 2.0       | 1.2       | 2.2                | 6.9       | 1.4              | 0.4        | 5.2               |
|                    |            | ♂   | 1.6       | 0.9       | 2.0                | 6.4       | 2.1              | 0.5        | 3.6               |
|                    |            | ♂   | 1.9       | 1.0       | 1.6                | 6.3       | 1.8              | 0.3        | 4.6               |
|                    |            | ♂   | 1.7       | 0.8       | 1.4                | 5.6       | 1.3              | 0.4        | NA                |
|                    |            | ♂   | 1.7       | 1.0       | 1.7                | 5.5       | 1.6              | 0.3        | NA                |
|                    |            | ♂   | 1.7       | 1.1       | 1.7                | 5.7       | 1.8              | 0.6        | NA                |

L & R: Left and Right Kidneys, Lungs and Kidneys; NA: Not Applicable.

S. typhi Ty21a expressing the HPV 16 and 18 L1 proteins as vaccine candidate. Intended clinical application of test compound is ‘oral route’, in view of non-colonisation of attenuated S. typhi Ty21a in laboratory animals, the sub-chronic toxicity of vaccine candidate was tested through oral route (as per regulatory guidelines) and innovative intranasal route [2, 3]. Since the test compounds is recombinant vaccine, due approvals from Institutional Biosafety Committee (IBSC) and Review Committee on Genetic Manipulation (RCGM), Department of Biotechnology (DBT), India were obtained for sub-chronic toxicity testing as per Schedule Y of Drug Controller General of India (DCGI) [4]. The prophylactic dose for Sprague Dawley (SD) rats (PD: 0.18 × 10⁶CFU/kg) and New Zealand White (NZW) rabbits (PD: 0.09 × 10⁶CFU/kg) were derived using pharmacological conversion factor [5] from adult human clinical dose (2 × 10⁹ CFU/kg/70 kg). The prophylactic doses were administered through oral and intranasal routes to rats (100μl) and rabbits (200μl), whereas the average dose (5×PD) was administered to rats (AD:0.9 × 10⁹CFU/kg) and rabbits (AD: 0.45 × 10⁹CFU/kg) through intranasal routes only.

The repeated dose effect of test compound was assessed through successive exposures on Day 1, Day 3 and Day 5 with specified routes. The effect of vector i.e. attenuated S. typhi Ty21a, was assessed in rats and rabbits by administration through oral and intranasal routes and represented as Experimental control groups. Similarly, the effect of vehicle i.e. phosphate buffer
| Group                          | Time Point | Sex | Brain (g) | Heart (g) | Kidney (L & R) (g) | Liver (L & R) (g) | Lungs (L & R) (g) | Spleen (g) | Testis (L & R) (g) |
|-------------------------------|------------|-----|-----------|-----------|-------------------|------------------|------------------|------------|-------------------|
| Vehicle Control               | 93rd Day   | ♂   | 1.6       | 1.4       | 1.2               | 9.9              | 2.2              | 0.6        | 5                 |
|                               |            |     | 1.2       | 1.1       | 2.2               | 7.4              | 2.2              | 0.4        | 4.4               |
|                               |            |     | 1.8       | 0.9       | 1.8               | 7.6              | 1.5              | 0.4        | 3.2               |
|                               |            |     | 1.7       | 1.3       | 2.2               | 8.9              | 1.7              | 0.4        | 3.2               |
|                               |            |     | 1.8       | 1.2       | 2.2               | 8.3              | 2.3              | 0.5        | 4.4               |
|                               |            | ♂   | 1.9       | 1.5       | 2.0               | 8.7              | 2.3              | 0.5        | 4.6               |
|                               |            |     | 1.9       | 0.9       | 1.9               | 5.9              | 1.2              | 0.4        | NA                |
|                               |            |     | 1.9       | 1.1       | 1.9               | 6.1              | 1.6              | 0.5        | NA                |
|                               |            | ♀   | 1.6       | 1.1       | 1.5               | 5.9              | 1.6              | 0.3        | NA                |
|                               |            |     | 1.4       | 0.8       | 1.9               | 6.1              | 2.3              | 0.5        | NA                |
|                               |            |     | 1.9       | 1.2       | 1.9               | 6.9              | 2.0              | 0.5        | NA                |
|                               |            |     | 1.9       | 1.1       | 2.0               | 7.0              | 2.3              | 0.4        | NA                |
| Experimental Control          | 93rd Day   | ♂   | 1.9       | 1.4       | 2.3               | 8.4              | 1.7              | 0.4        | 4.8               |
|                               |            |     | 1.8       | 1.1       | 2.5               | 8.1              | 1.9              | 0.4        | 3.8               |
|                               |            |     | 2.0       | 1         | 2.4               | 6.8              | 1.6              | 0.4        | 4.4               |
|                               |            |     | 1.8       | 1.2       | 2.3               | 8.2              | 2.1              | 0.5        | 5.2               |
|                               |            | ♂   | 1.8       | 0.8       | 2.3               | 8                | 2                | 0.4        | 4.6               |
|                               |            |     | 1.7       | 1.1       | 2.6               | 8.5              | 2                | 0.5        | 5.2               |
|                               |            | ♀   | 1.8       | 1.1       | 2               | 6.9              | 2.3              | 0.7        | NA                |
|                               |            |     | 1.6       | 1.2       | 1.7               | 6.2              | 2.1              | 0.5        | NA                |
|                               |            |     | 2.2       | 1         | 2.1               | 5.8              | 2.1              | 0.6        | NA                |
|                               |            |     | 1.8       | 1.1       | 1.7               | 6.2              | 1.7              | 0.4        | NA                |
|                               |            |     | 1.7       | 1.1       | 1.7               | 6.3              | 2.1              | 0.5        | NA                |
| Oral                          | 93rd Day   | ♂   | 1.7       | 1.2       | 2.1               | 8.6              | 1.8              | 0.3        | 4.9               |
|                               |            |     | 1.8       | 1.4       | 2.3               | 9.4              | 1.9              | 0.8        | 6.9               |
|                               |            |     | 1.9       | 1.5       | 2.5               | 8.7              | 2.0              | 0.6        | 5.4               |
|                               |            |     | 2.0       | 1.9       | 2.7               | 10.6             | 2.1              | 0.6        | 6.0               |
|                               |            |     | 2.0       | 1.3       | 2.2               | 8.7              | 1.8              | 0.5        | 5.1               |
|                               |            | ♂   | 1.5       | 1.4       | 2.9               | 10.2             | 2.0              | 0.5        | 6.4               |
|                               |            |     | 1.4       | 1         | 1.7               | 6.6              | 1.8              | 0.3        | NA                |
|                               |            |     | 2.2       | 0.9       | 1.8               | 7                | 1.5              | 0.6        | NA                |
|                               |            |     | 1.5       | 1.2       | 1.8               | 6.9              | 2.2              | 0.2        | NA                |
|                               |            |     | 1.9       | 1.0       | 2.1               | 7.2              | 1.7              | 0.6        | NA                |
|                               |            |     | 1.7       | 1.0       | 1.8               | 6.1              | 1.9              | 0.4        | NA                |
|                               |            |     | 1.9       | 1.2       | 2.1               | 8.0              | 1.7              | 0.6        | NA                |
| Prophylactic Dose (PD)        | 93rd Day   | ♂   | 1.6       | 2.5       | 2.9               | 9.8              | 2.8              | 0.7        | 5.2               |
|                               |            |     | 1.6       | 1.4       | 2.4               | 9.1              | 1.8              | 0.5        | 6.4               |
|                               |            |     | 1.6       | 2.2       | 2.3               | 9.2              | 1.9              | 0.4        | 6.0               |
|                               |            |     | 2.0       | 1.6       | 2.8               | 8.4              | 2.7              | 0.6        | 5.2               |
|                               |            | ♂   | 1.6       | 1.0       | 2.4               | 8.8              | 2.3              | 0.5        | 5.3               |
|                               |            |     | 1.8       | 1.4       | 2.2               | 8.3              | 1.7              | 0.5        | 5.2               |
|                               |            | ♀   | 1.8       | 1.1       | 2.1               | 7.4              | 2.0              | 0.4        | NA                |
|                               |            |     | 1.6       | 1.0       | 1.7               | 6.0              | 1.7              | 0.3        | NA                |
|                               |            |     | 1.8       | 0.8       | 2.0               | 8.3              | 2.1              | 0.6        | NA                |
|                               |            |     | 1.5       | 0.8       | 1.8               | 6.7              | 1.8              | 0.4        | NA                |
| Oral                          | 93rd Day   | ♂   | 1.7       | 1.6       | 1.9               | 8.1              | 2.1              | 0.6        | 4.5               |
|                               |            |     | 1.9       | 1.2       | 2.3               | 7.9              | 1.7              | 0.5        | 5.2               |
|                               |            |     | 1.7       | 1.8       | 2.3               | 11.4             | 1.7              | 0.8        | 3.8               |
|                               |            |     | 1.5       | 1.1       | 2.2               | 7.1              | 1.9              | 0.4        | 5.1               |
|                               |            |     | 1.6       | 1.1       | 2.0               | 7.6              | 2.4              | 0.4        | 4.8               |
|                               |            | ♂   | 1.5       | 1.6       | 2.3               | 7.6              | 2.2              | 0.4        | 4.7               |
|                               |            |     | 1.5       | 0.9       | 1.9               | 6.8              | 2.1              | 0.5        | NA                |
|                               |            |     | 1.7       | 0.7       | 1.8               | 6.5              | 1.3              | 0.5        | NA                |
|                               |            |     | 1.5       | 0.8       | 1.7               | 5.3              | 2.3              | 0.3        | NA                |
|                               |            |     | 1.7       | 0.9       | 1.7               | 7.3              | 1.5              | 0.5        | NA                |
|                               |            |     | 1.8       | 0.9       | 2.2               | 6.9              | 1.6              | 0.4        | NA                |
|                               |            |     | 1.9       | 1.4       | 1.7               | 5.5              | 1.8              | 0.3        | NA                |

(continued on next page)
saline (PBS), was assessed by administration through intranasal routes to rats and rabbits and represented as vehicle control groups. To unveil the test compound effect in relation with time was assessed by euthanizing 25% of animals on 15th day, another 25% animals on 29th Day and remaining animals on 93rd day of post-exposure of 1st dose. Blood was collected from retro-orbital plexus using microhematocrit capillaries (Fisher Scientific # 22–362,566) into K2EDTA tubes (BD Vacutainer) before euthanizing the animals, whereas vital organs were collected after euthanization. The body weights of animals were obtained periodically.

**Table 7.3 (continued)**

| Group                | Time Point | Sex | Brain (g) | Heart (g) | Kidney (L & R) (g) | Liver (g) | Lungs (L & R) (g) | Spleen (g) | Testis (L & R) (g) |
|----------------------|------------|-----|-----------|-----------|-------------------|-----------|------------------|------------|-------------------|
| Average Dose (IN)    | 93rd Day   | ♂   | 1.8       | 1.1       | 1.7               | 7.5       | 2.9              | 0.4        | 4.5               |
|                      |            | 1.9  | 1.5       | 2.6       | 9.2               | 1.9       | 0.7              | 3.3        |                   |
|                      |            | 1.9  | 1.5       | 2.2       | 8.8               | 2.0       | 0.6              | 4.8        |                   |
|                      |            | 1.9  | 1.2       | 2.6       | 9.6               | 1.7       | 0.5              | 7.4        |                   |
|                      |            | 1.7  | 1.2       | 2.4       | 8.1               | 2.1       | 0.4              | 3.4        |                   |
|                      |            | 1.7  | 1.3       | 2.2       | 8.3               | 2.0       | 0.7              | 4.7        |                   |
|                      |            | ♀   | 1.7       | 1.0       | 1.8               | 6.7       | 1.6              | 0.4        | NA                |
|                      |            | 1.9  | 1.0       | 2.0       | 7.5               | 2.5       | 0.6              | NA         |                   |
|                      |            | 1.7  | 0.9       | 1.8       | 7.1               | 1.6       | 0.5              | NA         |                   |
|                      |            | 1.7  | 1.1       | 1.9       | 6.8               | 2.0       | 0.5              | NA         |                   |
|                      |            | 1.8  | 1.2       | 1.6       | 5.5               | 1.8       | 0.4              | NA         |                   |
|                      |            | 1.6  | 1.1       | 1.7       | 6.6               | 2.0       | 0.4              | NA         |                   |

L & R: Left and Right Kidneys, Lungs and Testis; NA: Not Applicable.

**Table 8.1**

Organ Weights of rabbits Euthanized on 15th Day of Post-Exposure of recombinant HPV vaccine.

| Group                | Time Point | Sex | Brain (g) | Heart (g) | Kidney (L & R) (g) | Liver (g) | Lungs (L & R) (g) | Spleen (g) | Testis (L & R) (g) |
|----------------------|------------|-----|-----------|-----------|-------------------|-----------|------------------|------------|-------------------|
| Vehicle Control      | 15th Day   | ♂   | 7.7       | 4.8       | 9.3               | 48.8      | 7.5              | 0.9        | 2.5               |
|                      |            | 7.9  | 5.4       | 13.5      | 53.3              | 7.6       | 1.2              | 6.9        |                   |
|                      |            | 6.8  | 4.1       | 11.1      | 51.4              | 11.2      | 0.7              | 7.0        |                   |
|                      |            | ♀   | 9.2       | 6.8       | 13.4              | 52.8      | 9.4              | NA         |                   |
|                      |            | 8.7  | 5.9       | 11.6      | 59.6              | 11.8      | NA               | 9.0        |                   |
| Experimental Control | IN         | 15th Day | ♂   | 7.5       | 4.8       | 11.4              | 52.7      | 8.7              | 1.0        | 3.1               |
|                      |            | 9.0  | 6.6       | 13.0      | 63.7              | 15.7      | 1.6              | 6.5        |                   |
|                      |            | ♀   | 7.7       | 5.3       | 10.9              | 54.3      | 8.8              | NA         |                   |
|                      |            | 9.5  | 5.5       | 12.1      | 67.2              | 10.4      | 1.9              | NA         |                   |
| Oral                 | 15th Day   | ♂   | 9.3       | 7.5       | 12.9              | 84.6      | 9.9              | 2.6        | 5.4               |
|                      |            | 8.9  | 7.0       | 11.9      | 58.3              | 22.5      | 1.7              | 6.9        |                   |
|                      |            | ♀   | 8.3       | 8.2       | 12.9              | 45.9      | 11.6             | NA         |                   |
|                      |            | 7.8  | 6.6       | 11.7      | 65.7              | 8.7       | 0.8              | NA         |                   |
| Prophylactic Dose (PD) | IN         | 15th Day | ♂   | 9.4       | 6.0       | 16.8              | 67.8      | 11.7             | 1.8        | 8.9               |
|                      |            | 8.5  | 8.4       | 12.1      | 41.4              | 7.5       | 0.6              | 1.9        |                   |
|                      |            | 9.0  | 5.1       | 10.2      | 40.6              | 8.8       | 1.0              | 7.8        |                   |
|                      |            | ♀   | 6.4       | 5.5       | 8.6               | 31.7      | 5.7              | NA         |                   |
|                      |            | 8.1  | 9.1       | 14.6      | 57.8              | 11.8      | 1.3              | NA         |                   |
| Oral                 | 15th Day   | ♂   | 8.8       | 7.8       | 11.0              | 57.8      | 8.8              | 0.8        | 5.1               |
|                      |            | 7.7  | 7.1       | 10.3      | 43.8              | 10.3      | 0.7              | 5.9        |                   |
|                      |            | 7.4  | 4.3       | 11.3      | 42.4              | 6.9       | 0.5              | 5.1        |                   |
|                      |            | 9.1  | 6.6       | 14.2      | 79.1              | 13.2      | 2.1              | NA         |                   |
|                      |            | 6.3  | 5.0       | 10.3      | 50.6              | 11.1      | 1.2              | NA         |                   |
| Average Dose (IN)    | 15th Day   | ♂   | 7.6       | 7.0       | 12.7              | 58.9      | 8.8              | 1.0        | 4.9               |
|                      |            | 7.3  | 4.5       | 12.1      | 36.7              | 6.6       | 0.5              | 1.1        |                   |
|                      |            | 10.1 | 8.8       | 16.4      | 82.4              | 13.1      | 2.6              | 7.5        |                   |
|                      |            | ♀   | 7.4       | 6.6       | 11.1              | 43.4      | 9.6              | 2.0        | NA                |
|                      |            | 6.5  | 7.4       | 11.2      | 80.3              | 9.5       | 1.1              | NA         |                   |

L & R: Left and Right Kidneys, Lungs and Testis; NA: Not Applicable.
Table 8.2
Organ Weights of rabbits Euthanized on 29th Day of Post-Exposure of recombinant HPV vaccine.

| Group                        | Time Point | Sex | Brain (g) | Heart (g) | Kidney (L & R) (g) | Liver (g) | Lungs (L & R) (g) | Spleen (g) | Testis (L & R) (g) |
|------------------------------|------------|-----|-----------|-----------|-------------------|-----------|-------------------|------------|-------------------|
| Vehicle Control              | 29th Day   | ♂   | 7.4       | 3.9       | 11.7              | 45.2      | 7.3               | 0.2        | 4.8               |
|                              |            | ♀   | 9.3       | 8.9       | 16.0              | 60.7      | 9.7               | 1.2        | 7.0               |
|                              |            |     | 6.5       | 5.0       | 11.8              | 51.4      | 10.9              | 0.8        | NA                |
|                              |            |     | 7.1       | 4.5       | 9.4               | 41.4      | 8.1               | 0.9        | NA                |
|                              |            |     | 9.3       | 6.5       | 12.8              | 58.0      | 11.9              | 1.2        | NA                |
| Experimental Control         | IN 29th Day| ♂   | 7.3       | 6.2       | 11.6              | 63.6      | 13.6              | 0.6        | 7.7               |
|                              |            | ♀   | 3.4       | 2.9       | 7.9               | 45.0      | 4.4               | 0.2        | 4.4               |
|                              |            |     | 7.9       | 6.5       | 11.0              | 57.1      | 6.7               | 0.9        | NA                |
|                              |            |     | 8.8       | 6.6       | 14.2              | 75.0      | 11.5              | 0.8        | NA                |
|                              |            |     | 5.9       | 9.4       | 9.9               | 58.2      | 7.5               | 0.8        | NA                |
| Oral                         | 29th Day   | ♂   | 8.3       | 6.0       | 13.7              | 61.8      | 12.1              | 0.6        | 5.0               |
|                              |            | ♀   | 7.0       | 6.5       | 11.7              | 68.6      | 10.5              | 2.0        | 4.6               |
|                              |            |     | 8.4       | 6.7       | 11.3              | 55.8      | 8.0               | 0.8        | NA                |
|                              |            |     | 7.3       | 6.0       | 14.3              | 59.3      | 13.2              | 1.3        | NA                |
|                              |            |     | 6.0       | 5.2       | 9.9               | 66.1      | 9.4               | 1.1        | NA                |
| Prophylactic Dose (PD)       | IN 29th Day| ♂   | 7.7       | 8.9       | 12.5              | 61.2      | 9.4               | 0.9        | 7.0               |
|                              |            | ♀   | 8.0       | 6.9       | 12.9              | 75.6      | 10.5              | 0.5        | 7.2               |
|                              |            |     | 8.9       | 7.9       | 11.9              | 62.5      | 8.3               | 1.3        | NA                |
|                              |            |     | 8.5       | 4.9       | 14.2              | 63.9      | 10.3              | 1.5        | NA                |
|                              |            |     | 8.5       | 4.7       | 10.1              | 48.5      | 12.3              | 1.0        | NA                |
| Oral                         | 29th Day   | ♂   | 8.6       | 3.9       | 10.1              | 45.1      | 5.8               | 0.4        | 4.8               |
|                              |            | ♀   | 8.0       | 6.0       | 13.5              | 79.1      | 12.9              | 1.2        | 6.9               |
|                              |            |     | 7.9       | 5.1       | 14.1              | 61.2      | 9.4               | 0.7        | NA                |
|                              |            |     | 6.6       | 6.3       | 11.2              | 68.6      | 7.9               | 1.1        | NA                |
|                              |            |     | 8.5       | 4.7       | 10.5              | 62.2      | 9.4               | 0.9        | NA                |
| Average Dose (IN)            | 29th Day   | ♂   | 8.0       | 5.0       | 12.0              | 62.7      | 9.5               | 0.8        | 7.0               |
|                              |            | ♀   | 8.6       | 6.3       | 12.8              | 67.1      | 10.2              | 1.1        | 5.2               |
|                              |            |     | 7.7       | 4.1       | 9.5               | 49.0      | 8.6               | 0.8        | NA                |
|                              |            |     | 7.3       | 5.7       | 12.8              | 73.6      | 9.5               | 1.9        | NA                |
|                              |            |     | 8.0       | 4.5       | 10.0              | 54.0      | 8.1               | 0.8        | NA                |

L & R: Left and Right Kidneys, Lungs and Testis; NA: Not Applicable.

Blood samples were analysed for haemoglobin, indices of red blood cells, differential leucocyte count and total leucocyte count using automated blood cell counter as per the manufacturer’s instructions and guidelines (Serono Baker System 9120 CP+, USA) [6]. The biochemical profile viz. ALT, AST, ALP, creatinine, total bilirubin, urea, glucose, calcium, total protein and albumin levels were determined in serum samples using ACE™ clinical autoanalyzer (Model Acelera). Whereas, the weights of vital organs were recorded using analytical balance (Sartorius, SECURA125–10BR). The genotoxic effect of rSt.HPV expressing HPV 16 and 18 L1 proteins, if any were determined in rats and rabbits used for sub-chronic toxicity testing through bone marrow micronucleus assay. Mice were used to determine the immune response in terms of specific IgG levels and allergenicity in terms of specific IgE levels were assessed using standard ELISA method. The raw data of all the animals euthanized at different time points were compiled and computed according to the groups.
Table 8.3
Organ Weights of rabbits Euthanized on 93rd Day of Post-Exposure of recombinant HPV vaccine.

| Group                      | Time Point | Sex | Brain (g) | Heart (g) | Kidney (L & R) (g) | Liver (g) | Lungs (L & R) (g) | Spleen (g) | Testis (L & R) (g) |
|----------------------------|------------|-----|-----------|-----------|-------------------|-----------|------------------|-----------|-------------------|
| Vehicle Control            | 93rd Day   | ♂   | 7.9       | 5.4       | 10.9              | 65.3      | 7.9              | 0.8       | 7.4               |
|                           |            |     | 8.1       | 5.0       | 8.6               | 51.5      | 7.7              | 0.8       | 6.6               |
|                           |            |     | 7.9       | 7.7       | 8.3               | 62.6      | 10.3             | 1.3       | 5.8               |
|                           |            |     | 9.5       | 5.6       | 11.0              | 61.5      | 8.6              | 0.9       | 6.8               |
|                           |            |     | 8.1       | 5.1       | 10.1              | 41.9      | 9.1              | 0.5       | 7.5               |
|                           |            |♀    | 8.6       | 4.9       | 10.2              | 51.1      | 11.5             | 0.6       | NA                |
|                           |            |♀    | 8.8       | 6.6       | 11.2              | 54.0      | 12.3             | 1.3       | NA                |
|                           |            |♀    | 7.1       | 5.1       | 11.3              | 59.8      | 7.8              | 1.2       | NA                |
|                           |            |♀    | 9.5       | 5.4       | 11.1              | 54.6      | 11.3             | 1.6       | NA                |
| Experimental Control      | IN 93rd Day| ♂   | 8.9       | 6.9       | 10.9              | 51.9      | 11.8             | 1.3       | NA                |
|                           |            |     | 8.1       | 5.0       | 9.5               | 54.3      | 10.2             | 1.1       | 8.2               |
|                           |            |♀    | 8.3       | 4.8       | 8.7               | 47.7      | 11.1             | 0.7       | 9.5               |
|                           |            |♀    | 8.1       | 5.5       | 10.4              | 54.5      | 8.9              | 0.4       | 8.8               |
|                           |            |♀    | 9.3       | 7.2       | 14.0              | 81.0      | 10.9             | 1.6       | 7.8               |
|                           |            |♀    | 8.9       | 6.4       | 9.7               | 55.5      | 13.2             | 0.9       | 9.7               |
|                           |            |♀    | 9.3       | 9.2       | 14.7              | 65.1      | 10.7             | 1.0       | 3.7               |
| Oral 93rd Day             |            |♂    | 8.6       | 4.9       | 12.1              | 52.1      | 8.7              | 1.4       | NA                |
|                           |            |♀    | 8.3       | 4.9       | 8.8               | 45.9      | 8.7              | 1.1       | NA                |
|                           |            |♀    | 9.1       | 5.5       | 10.3              | 45.4      | 9.4              | 1.0       | NA                |
|                           |            |♀    | 8.3       | 8.6       | 9.8               | 60.2      | 10.9             | 1.7       | NA                |
| Prophylactic Dose (PD)    | IN 93rd Day|♂    | 7.9       | 5.4       | 13.1              | 57.0      | 8.5              | 0.9       | 5.5               |
|                           |            |♀    | 8.6       | 8.6       | 13.7              | 64.0      | 12.7             | 0.7       | 7.3               |
|                           |            |♀    | 9.0       | 5.5       | 10.1              | 55.1      | 8.8              | 0.6       | 7.9               |
|                           |            |♀    | 9.5       | 6.0       | 9.3               | 57.6      | 6.0              | 1.5       | 9.0               |
|                           |            |♀    | 6.7       | 4.5       | 11.5              | 55.5      | 12.5             | 1.1       | 5.5               |
|                           |            |♀    | 8.5       | 5.7       | 10.6              | 66.6      | 10.4             | 10.3      | NA                |
|                           |            |♀    | 10.1      | 6.1       | 13.0              | 55.4      | 10.5             | 0.9       | NA                |
|                           |            |♀    | 8.1       | 6.4       | 11.5              | 60.7      | 12.1             | 1.7       | NA                |
|                           |            |♀    | 9.0       | 4.5       | 10.3              | 49.6      | 8.5              | 0.8       | NA                |
|                           |            |♀    | 8.8       | 4.8       | 12.5              | 52.8      | 12.6             | 1.0       | NA                |
| Oral 93rd Day             |            |♂    | 9.5       | 5.0       | 10.2              | 58.7      | 9.7              | 1.1       | 5.6               |
|                           |            |♀    | 8.9       | 5.8       | 12.5              | 64.5      | 13.8             | 0.6       | 8.6               |
|                           |            |♀    | 7.7       | 6.4       | 10.1              | 72.3      | 1.6              | 1.1       | 9.9               |
|                           |            |♀    | 7.4       | 6.9       | 10.3              | 59.6      | 11.3             | 0.9       | 8.7               |
|                           |            |♀    | 8.7       | 5.9       | 11.9              | 63.0      | 14.2             | 0.6       | 9.0               |
|                           |            |♀    | 6.9       | 5.7       | 12.3              | 57.3      | 11.0             | 0.7       | NA                |
|                           |            |♀    | 9.0       | 6.3       | 13.3              | 73.0      | 10.8             | 0.8       | NA                |
|                           |            |♀    | 8.1       | 5.1       | 8.4               | 40.4      | 9.2              | 1.2       | NA                |
|                           |            |♀    | 9.8       | 5.7       | 10.2              | 45.7      | 9.8              | 9.2       | NA                |
|                           |            |♀    | 9.3       | 6.8       | 11.8              | 60.8      | 10.7             | 1.1       | NA                |
| Average Dose (IN)         | 93rd Day   |♂    | 8.4       | 4.8       | 10.0              | 62.1      | 11.2             | 0.9       | 7.9               |
|                           |            |♀    | 5.8       | 5.5       | 10.2              | 54.2      | 8.1              | 0.6       | 7.2               |
|                           |            |♀    | 8.1       | 6.3       | 11.4              | 66.3      | 16.2             | 1.1       | 5.8               |
|                           |            |♀    | 9.3       | 5.1       | 11.4              | 56.7      | 10.5             | 1.1       | 7.3               |
|                           |            |♀    | 9.0       | 6.1       | 9.3               | 50.6      | 7.5              | 0.7       | 9.9               |
|                           |            |♀    | 8.2       | 5.6       | 17.5              | 77.3      | 16.0             | 3.2       | NA                |
|                           |            |♀    | 8.2       | 8.3       | 9.2               | 52.1      | 13.0             | 1.5       | NA                |
|                           |            |♀    | 7.8       | 5.4       | 10.8              | 54.0      | 9.5              | 1.3       | NA                |
|                           |            |♀    | 9.0       | 5.6       | 9.4               | 76.0      | 8.6              | 0.8       | NA                |
|                           |            |♀    | 9.0       | 5.8       | 11.1              | 53.5      | 13.1             | 1.2       | NA                |

L & R: Left and Right Kidneys, Lungs and Testis; NA: Not Applicable.
Table 9
The data of Bone Marrow Micronucleus of rats exposed with rSt.HPV expressing HPV 16 and 18 L1 Proteins as part of Sub-chronic Testing.

| Parameter          | Euthanization Day | Sex | Vehicle Control (VC) | Experimental Control (EC) | Prophylactic Dose (PD) | Average Dose - Intra-Nasal (IN) |
|--------------------|-------------------|-----|---------------------|---------------------------|------------------------|---------------------------------|
|                    |                   |     | Intra-Nasal         | Intra-Nasal                | Oral                   | Oral                            |
|                    |                   |     | (IN)                |                           |                        |                                 |
| PCE per 200 NCE    | 15th Day          | ♂   | 0.59                | 0.16                      | 0.74                   | 0.78                            | 0.79                            | 0.81                           |
|                    |                   |     | 0.99                | 0.95                      | 0.76                   | 0.92                            | 0.81                            | 0.93                           |
|                    |                   | ♂   | 0.74                | 0.89                      | 0.74                   | 0.96                            | 0.87                            | 0.97                           |
|                    |                   |     | 1.03                | 0.99                      | 0.91                   | 1.04                            | 1.01                            | 0.94                           |
|                    |                   | ♂   | 1.06                | 0.92                      | 1.17                   | 0.87                            | 0.98                            | 1.04                           |
|                    |                   |     | 1.10                | 0.96                      | 1.06                   | 0.91                            | 0.92                            | 0.77                           |
|                    | 29th Day          | ♂   | 0.91                | 0.99                      | 1.07                   | 0.89                            | 0.96                            | 1.09                           |
|                    |                   |     | 0.84                | 1.17                      | 0.97                   | 0.97                            | 1.05                            | 1.06                           |
|                    |                   | ♂   | 1.07                | 1.34                      | 0.98                   | 0.93                            | 1.07                            | 1.17                           |
|                    |                   |     | 1.24                | 1.02                      | 0.97                   | 0.89                            | 0.74                            | 0.94                           |
|                    |                   | ♂   | 1.09                | 1.06                      | 0.92                   | 0.92                            | 0.82                            | 0.88                           |
|                    |                   |     | 1.10                | 1.03                      | 0.91                   | 0.84                            | 0.92                            | 0.87                           |
|                    | 93rd Day          | ♂   | 0.99                | 1.12                      | 1.07                   | 0.97                            | 0.93                            | 0.92                           |
|                    |                   |     | 0.97                | 1.17                      | 1.06                   | 0.96                            | 0.87                            | 0.74                           |
|                    |                   | ♂   | 1.21                | 1.23                      | 0.82                   | 0.86                            | 0.96                            | 0.82                           |
|                    |                   |     | 1.16                | 1.05                      | 0.88                   | 0.96                            | 0.91                            | 0.82                           |
|                    |                   | ♂   | 0.97                | 1.07                      | 0.92                   | 0.80                            | 0.99                            | 0.91                           |
|                    |                   |     | 0.74                | 1.06                      | 0.91                   | 0.86                            | 0.71                            | 0.96                           |
|                    |                   | ♂   | 0.97                | 1.06                      | 1.31                   | 1.17                            | 1.05                            | 0.98                           |
|                    |                   |     | 0.96                | 1.16                      | 1.20                   | 1.15                            | 1.14                            | 0.87                           |
|                    |                   | ♂   | 1.13                | 1.12                      | 1.14                   | 1.09                            | 0.74                            | 0.91                           |
|                    |                   |     | 0.88                | 0.69                      | 0.82                   | 1.10                            | 0.99                            | 0.91                           |
|                    |                   | ♂   | 0.09                | 0.74                      | 0.80                   | –                                | 0.92                            | 0.67                           |
|                    |                   |     | 0.96                | –                         | 0.86                   | –                                | 0.82                            | 0.92                           |
| MNPCE per 2000PCE  | 15th Day          | ♂   | 0.60                | 1.40                      | 0.70                   | 1.20                            | 1.70                            | 1.30                           |
|                    |                   |     | 0.90                | 1.20                      | 0.40                   | 1.40                            | 2.10                            | 1.70                           |
|                    |                   | ♂   | 0.50                | 0.80                      | 0.60                   | 1.50                            | 1.60                            | 1.90                           |
|                    |                   |     | 0.60                | 0.30                      | 0.70                   | 0.70                            | 1.40                            | 0.70                           |
|                    |                   | ♂   | 1.50                | 0.40                      | 0.60                   | 0.90                            | 1.10                            | 1.20                           |
|                    |                   |     | 0.50                | 0.20                      | 0.50                   | 1.20                            | 1.60                            | 0.80                           |
|                    | 29th Day          | ♂   | 0.60                | 0.50                      | 1.00                   | 1.00                            | 1.50                            | 1.70                           |
|                    |                   |     | 0.70                | 0.50                      | 1.20                   | 1.20                            | 0.90                            | 1.60                           |
|                    |                   | ♂   | 0.90                | 0.40                      | 1.10                   | 1.60                            | 1.30                            | 1.50                           |
|                    |                   |     | 0.90                | 1.30                      | 0.90                   | 0.50                            | 0.70                            | 0.70                           |
|                    |                   | ♂   | 0.70                | 1.00                      | 0.10                   | 0.90                            | 0.90                            | 1.20                           |
|                    |                   |     | 0.60                | 1.10                      | 0.40                   | 0.60                            | 0.65                            | 1.40                           |
|                    | 93rd Day          | ♂   | 0.60                | 0.40                      | 0.90                   | 1.40                            | 1.20                            | 0.60                           |
|                    |                   |     | 0.90                | 0.70                      | 1.05                   | 1.30                            | 1.20                            | 1.50                           |
|                    |                   | ♂   | 0.70                | 0.30                      | 0.50                   | 1.70                            | 1.30                            | 1.60                           |
|                    |                   |     | 0.50                | 0.30                      | 0.60                   | 1.40                            | 1.10                            | 1.20                           |
|                    |                   | ♂   | 0.50                | 0.60                      | 0.70                   | 1.20                            | 1.00                            | 2.10                           |
|                    |                   |     | 0.20                | 0.70                      | 0.80                   | 1.40                            | 1.20                            | 1.40                           |
|                    |                   | ♂   | 1.30                | 0.60                      | 1.30                   | 1.60                            | 0.50                            | 0.70                           |
|                    |                   |     | 1.20                | 0.50                      | 0.90                   | 1.50                            | 0.60                            | 1.40                           |
|                    |                   | ♂   | 1.00                | 1.20                      | 0.85                   | 1.30                            | 1.30                            | 1.90                           |
|                    |                   |     | 1.20                | 1.30                      | 1.10                   | 1.00                            | 1.40                            | 1.30                           |
|                    |                   | ♂   | 1.10                | 1.20                      | 0.60                   | –                                | 1.70                            | 1.20                           |
|                    |                   |     | 1.00                | –                         | 0.50                   | –                                | 1.60                            | 1.40                           |
| Parameter            | Euthanization Day | Sex | Vehicle Control (VC) | Experimental Control (EC) | Prophylactic Dose (PD) | Average Dose – Intra-Nasal (IN) |
|----------------------|-------------------|-----|----------------------|---------------------------|------------------------|--------------------------------|
|                      |                   |     |                      | 15th Day                  |                        |                                 |
|                      |                   | ♂   | 212 216 198 174 162 176 | 241 236 186 168 182 167 |                        |                                 |
|                      |                   |     | 228 – – 194 190 184 | 196 192 158 198 194 201 |                        |                                 |
|                      |                   | ♂   | 228 188 147 182 196 206 | 182 188 147 182 196 206 |                        |                                 |
|                      |                   |     | 29th Day              |                           |                        |                                 |
|                      |                   | ♂   | 216 202 185 168 206 204 | 228 198 192 194 207 202 |                        |                                 |
|                      |                   |     | 238 194 184 198 168 164 | 248 186 205 174 176 182 |                        |                                 |
|                      |                   | ♂   | 214 192 202 184 145 174 | 248 186 205 174 176 182 |                        |                                 |
|                      |                   |     | 93rd Day               |                           |                        |                                 |
|                      |                   | ♂   | 199 134 146 168 186 194 | 196 148 167 148 146 156 |                        |                                 |
|                      |                   |     | 146 146 120 194 128 122 | 128 165 182 142 194 130 |                        |                                 |
|                      |                   | ♂   | 156 134 174 192 164 166 | 206 174 188 162 208 184 |                        |                                 |
|                      |                   |     | 29th Day               |                           |                        |                                 |
|                      |                   | ♂   | 207 142 143 122 147 164 | 172 216 146 160 158 163 |                        |                                 |
|                      |                   |     | 176 144 132 132 132 188 | 207 142 143 122 147 164 |                        |                                 |
|                      |                   | ♂   | 93rd Day               |                           |                        |                                 |
|                      |                   |     | 176 144 132 132 132 188 | 207 142 143 122 147 164 |                        |                                 |
|                      |                   |     | 15th Day               |                           |                        |                                 |
|                      |                   | ♂   | 34 34 42 34 26 20      | 34 34 42 34 26 20        |                        |                                 |
|                      |                   |     | 32 – – 28 22 27       | 32 – – 28 22 27          |                        |                                 |
|                      |                   | ♂   | 29th Day               |                           |                        |                                 |
|                      |                   |     | 34 42 24 28 26 34     | 34 42 24 28 26 34       |                        |                                 |
|                      |                   | ♂   | 18 20 34 30 24 34     | 18 20 34 30 24 34       |                        |                                 |
|                      |                   |     | 34 34 34 30 10 12     | 34 34 34 30 10 12       |                        |                                 |
|                      |                   | ♂   | 12 32 42 30 16 16     | 12 32 42 30 16 16       |                        |                                 |
|                      |                   |     | 29th Day               |                           |                        |                                 |
|                      |                   | ♂   | 17 14 17 18 22 12     | 17 14 17 18 22 12       |                        |                                 |
|                      |                   |     | 16 15 18 10 26 12     | 16 15 18 10 26 12       |                        |                                 |
|                      |                   | ♂   | 93rd Day               |                           |                        |                                 |
|                      |                   |     | 26 10 14 12 18 18     | 26 10 14 12 18 18       |                        |                                 |
|                      |                   | ♂   | 8 24 6 20 32 42       | 8 24 6 20 32 42         |                        |                                 |
|                      |                   |     | 34 34 24 30 13 14     | 34 34 24 30 13 14       |                        |                                 |
|                      |                   | ♂   | 14 21 20 – – 18 26    | 14 21 20 – – 18 26      |                        |                                 |
### Table 11
Specific IgG levels against rSt.HPV 16 and 18 expressing L1 proteins in mice.

| Route of Administration | Euthanization Day | Vehicle Control OVA 1x HPV 5x HPV | Vehicle Control OVA 1x HPV 5x HPV |
|-------------------------|------------------|-----------------------------------|-----------------------------------|
| Intra-Nasal Route       | 0th Day          | 0.0762 0.1293 0.0636 0.0679       | 0.0732 0.1293 0.0594 0.0845       |
|                         |                  | 0.0569 0.1343 0.0624 0.0643       | 0.0787 0.1343 0.0662 0.0812       |
|                         |                  | 0.0614 0.1403 0.0531 0.0515       | 0.0715 0.1403 0.0821 0.0626       |
|                         |                  | 0.074   – 0.0597 0.0655           | 0.0771 0.092 0.0812              |
|                         |                  | 0.062   – 0.06   0.0633           | 0.0782 0.0741 0.0667             |
|                         |                  | 0.0721   – 0.0569 0.064   | 0.1179 0.0904 0.07               |
|                         | 28th Day         | 0.053   0.1676 0.0628 0.0948      | 0.1315 0.1676 0.0789 0.0893       |
|                         |                  | 0.0794 0.1946 0.0883 0.0784      | 0.1347 0.1946 0.1283 0.2068       |
|                         |                  | 0.0758 0.2138 0.08   0.0794      | 0.1512 0.2138 0.141 0.337         |
|                         |                  | 0.0884   – 0.0759 0.089          | 0.1551 0.121 0.6167              |
|                         |                  | 0.0762   – 0.0814 0.1253      | 0.1191 – 0.1111 –              |
|                         |                  | 0.0762   – 0.0816 –           | 0.1171 – 0.1111 –              |
|                         | 56th Day         | 0.1193 0.2913 0.0499 0.5304      | 0.1094 0.2913 0.116 0.6343       |
|                         |                  | 0.1364 0.3678 0.0972 0.1214      | 0.1498 0.3678 0.1138 0.6662       |
|                         |                  | 0.1087 0.2602 0.1846 0.307       | 0.1268 0.2602 0.1577 0.874       |
|                         |                  | 0.138   0.4617 0.0937 0.1482     | 0.1554 0.4617 0.1067 0.8688      |
|                         |                  | 0.1319 0.5098 0.0466 0.1417      | 0.1157 – 0.1111 –              |
|                         |                  | 0.1319 0.4197 0.0922 –          | 0.1201 – 0.1201 –              |
|                         | 63rd Day         | 0.1603 0.543 0.1942 1.2392       | 0.2261 0.543 0.2291 0.6683       |
|                         |                  | 0.2028 0.5376 0.1221 0.1473      | 0.2245 0.5376 0.2508 0.5359       |
|                         |                  | 0.1639 0.5036 0.1626 0.7843      | 0.2033 0.5036 0.1802 1.0143       |
|                         |                  | 0.1445 0.5257 0.1557 0.1856      | 0.1712 0.5257 0.5284 1.0121       |
|                         |                  | 0.1666 0.6643 0.1434 0.2724      | 0.1877 – 0.1877 –              |
|                         |                  | 0.1387   – 0.1387 –          | 0.2256 – 0.2256 –              |
|                         | 78th Day         | 0.1436 0.497 0.1238 0.6433       | 0.1171 0.497 0.1185 0.9733       |
|                         |                  | 0.0989 0.6288 0.1178 0.1627      | 0.1253 0.6288 0.1044 0.9769       |
|                         |                  | 0.4594 0.1685 –            | 0.4594 0.1623 –              |

(continued on next page)
Table 11 (continued)

| Route of Administration | Euthanization Day | Anti-HPV 16 L1 IgG | Anti-HPV 18 IgG |
|-------------------------|------------------|-------------------|-----------------|
|                         |                  | Vehicle Control   | OVA | 1x HPV | 5x HPV | Vehicle Control | OVA | 1x HPV | 5x HPV |
| Intra-Peritoneal        | 0th Day          | 0.0702            | 0.1731 | 0.0754 | 0.0624 | 0.0781 | 0.1731 | 0.0988 | 0.0802 |
| Administration          |                  | 0.0667            | 0.1881 | 0.0584 | 0.0602 | 0.0914 | 0.1881 | 0.0882 | 0.0811 |
|                         |                  | 0.0584            | 0.1984 | 0.0577 | 0.0544 | 0.091  | 0.1984 | 0.0732 | 0.0885 |
|                         |                  | 0.0739            | –     | 0.0564 | 0.0597 | 0.0862 | –     | 0.0631 | 0.1068 |
|                         |                  | 0.0593            | –     | 0.0619 | 0.0571 | 0.0735 | –     | 0.0694 | 0.0885 |
|                         | 14th Day         | 0.1128            | 0.4483 | 0.0841 | 0.0608 | 0.1579 | 0.4483 | 0.1335 | 0.1769 |
|                         |                  | 0.0649            | 0.6038 | 0.0761 | 0.053  | 0.1166 | 0.6038 | 0.1489 | 0.1353 |
|                         |                  | 0.0756            | 0.6972 | 0.0599 | 0.0555 | 0.096  | 0.6972 | 0.1145 | 0.1771 |
|                         |                  | 0.076             | 1.1227 | 0.0617 | 0.0547 | 0.1083 | 1.1227 | 0.1108 | 0.1553 |
|                         |                  | 0.0734            | 0.6326 | 0.0672 | 0.083  | 0.1477 | 0.6326 | 0.1151 | 0.1314 |
|                         |                  | 0.0626            | –     | 0.0673 | 0.0481 | 0.1402 | –     | 0.1451 | 0.1317 |
| 28th Day                |                  | 0.0627            | 0.3863 | 0.0542 | 0.0715 | 0.0745 | 0.3863 | 0.0984 | 0.1066 |
|                         |                  | 0.0736            | 0.5717 | 0.0537 | 0.0772 | 0.091  | 0.5717 | 0.0935 | 0.1324 |
|                         |                  | 0.0624            | 0.6917 | 0.082  | 0.0505 | 0.0876 | 0.6917 | 0.1226 | 0.1221 |
Table 12  
Allergenicity profile i.e. specific IgE levels against rSt.HPV 16 and 18 expressing L1 proteins in mice.

| Route of Administration | Euthanization Day | Anti-HPV 16 L1 IgE | Anti-HPV 18 IgE |
|-------------------------|------------------|--------------------|----------------|
|                         |                  | Vehicle Control | OVA  | 1x HPV | 5x HPV | Vehicle Control | OVA  | 1x HPV | 5x HPV |
| Intra-Nasal Route       | 0th Day          | 0.0045           | 0.0045 | 0.0162 | 0.0050 | 0.0051           | 0.0048 | 0.0103 | 0.0047 |
|                         |                  | 0.0104           | 0.0025 | 0.0014 | 0.0068 | 0.0080           | 0.0028 | 0.0018 | 0.0075 |
|                         |                  | 0.0122           | 0.0017 | 0.0168 | 0.0123 | 0.0069           | 0.0020 | 0.0150 | 0.0060 |
|                         |                  | 0.0147           | 0.0025 | 0.0040 | 0.0167 | 0.0091           | 0.0028 | 0.0026 | 0.0092 |
|                         |                  | 0.0026           | 0.0026 | 0.0064 | 0.0129 | -                | 0.0029 | 0.0039 | 0.0085 |
|                         |                  |                  | 0.0033 | 0.0050 | -      |                  | 0.0036 | -      | -      |
|                         | 28th Day         | 0.0057           | -0.001 | 0.0033 | 0.0033 | 0.0079           | 0.0002 | 0.0037 | 0.0004 |
|                         |                  | 0.0032           | -0.0012 | -0.0004 | -     | 0.0026           | -0.0009 | 0.0002 | 0.0025 |
|                         |                  | 0.0030           | 0.0023 | 0.0018 | -      | 0.0047           | 0.0026 | 0.0021 | 0.0010 |
|                         |                  |                  | -      | 0.0010 | -      |                  | -      | 0.0006 | 0.0013 |
|                         |                  |                  | -      | 0.0017 | 0.0013 | -                | -      | 0.0020 | 0.0015 |
|                         |                  |                  | -      | 0.0010 | 0.0003 | -                | -      | 0.0030 | 0.0015 |
|                         | 56th Day         | 0.0047           | -0.0002 | 0.0015 | -0.0006 | 0.0052           | -0.0001 | 0.0001 | 0.0024 |
|                         |                  | 0.0026           | -0.0004 | 0.0032 | 0.0035 | 0.0034           | 0.0014 | 0.0028 | 0.0021 |
|                         |                  | 0.0029           | 0.0011 | 0.0017 | -      | 0.0029           | 0.0020 | -0.0012 | -      |
|                         |                  |                  | -      | 0.0017 | 0.0056 | -                | 0.0012 | 0.0008 | 0.0014 |
|                         |                  |                  | -      | 0.0005 | 0.0040 | -                | 0.0024 | 0.0002 | 0.0069 |
|                         |                  |                  | -      | -      | -      |                  | -      | 0.0001 | -      |
|                         | 63rd Day         | 0.0009           | -0.0006 | 0.0010 | -0.0001 | 0.0004           | -0.0003 | 0.0588 | 0.0001 |
|                         |                  | 0.0024           | -0.0001 | 0.0014 | 0.0019 | -0.0005           | 0.0002 | -0.0006 | 0.0002 |
|                         |                  | 0.0011           | -0.0016 | 0.0016 | 0.0018 | -0.0015           | -0.0013 | 0.0005 | -0.0003 |
|                         |                  | 0.0012           | 0.0005 | 0.0026 | -      | -0.0017           | 0.0008 | 0.0020 | -      |
|                         |                  |                  | -      | 0.0000 | -      |                  | 0.0003 | -0.0015 | -      |
|                         |                  |                  | -      | 0.0009 | -      |                  | 0.0012 | 0.0025 | -      |
|                         | 73rd Day         | 0.0061           | 0.0000 | 0.0225 | 0.0003 | 0.0001           | 0.0003 | 0.0004 | 0.0018 |
|                         |                  | -0.0018          | 0.0004 | -0.0005 | -0.0005 | -0.0004           | 0.0007 | -0.0033 | 0.0019 |
|                         |                  |                  | -      | -0.0008 | -      |                  | -      | -0.0005 | -      |

(continued on next page)
| Route of Administration | Euthanization Day | Anti-HPV 16 L1 IgE | Anti-HPV 18 IgE |
|-------------------------|-------------------|------------------|----------------|
|                         | Vehicle Control   | OVA              | 1x HPV         | 5x HPV         | Vehicle Control   | OVA              | 1x HPV         | 5x HPV         |
| Intra-Peritoneal         | 0th Day           | 0.1531           | 0.1504         | 0.1227         | 0.1535           | 0.1729           | 0.1504         | 0.1522         | 0.1777         |
| Administration          |                   | 0.1718           | 0.1471         | 0.122          | 0.1623           | 0.2098           | 0.1471         | 0.1484         | 0.1666         |
|                         |                   | –                | 0.1699         | –              | –                | –                | 0.1699         | –              | –              |
|                         | 14th Day          | 0.1793           | 0.2897         | 0.1709         | 0.2089           | 0.1959           | 0.2897         | 0.1785         | 0.2258         |
|                         |                   | 0.2194           | 0.4485         | 0.1842         | 0.1997           | 0.2637           | 0.4485         | 0.1849         | 0.2206         |
|                         |                   | –                | 0.5106         | –              | –                | –                | 0.5106         | –              | –              |
|                         |                   | –                | 0.4622         | –              | –                | –                | 0.4622         | –              | –              |
|                         |                   | –                | 0.3672         | –              | –                | –                | 0.3672         | –              | –              |
|                         | 28th Day          | 0.1759           | 0.2589         | 0.1711         | 0.1901           | 0.1871           | 0.2589         | 0.1497         | 0.2021         |
|                         |                   | 0.2141           | 0.3641         | 0.1645         | 0.1768           | 0.1418           | 0.3641         | 0.1481         | 0.1908         |
|                         |                   | –                | 0.3954         | –              | –                | –                | 0.3954         | –              | –              |
Ethics Statement

The test compound of current article is genetically engineered \textit{S. typhi} Ty21a vector comprising of HPV 16 and 18 L1 protein coding genes; hence the sub-chronic testing was undertaken after obtaining the approvals from Institutional Bio-safety Committee (IBSC) and Review Committee on Genetic Manipulation (RCGM– DBT, India) [4]. In addition, the study design and experimental procedures followed for sub-chronic testing of recombinant HPV vaccine were approved by the Institutional Animal Ethics Committee (IAEC) (IAEC/Proj/08/21,012,008) of ICMR-National Institute of Nutrition, Hyderabad, India.

CRediT Author Statement

\textbf{Srinivasa Reddy Y.}: Experimental execution and data compilation along with manuscript preparation and communication; \textbf{Narendra Babu K.}: Immunological and allergenicity profile execution, compilation and interpretation; \textbf{Uday Kumar P.}: Supervision of haematological and histopathological examination; \textbf{Qadri S.S.Y.H.}: Animal health monitoring and interpretation of test compound effect, if any during the course of experiment; \textbf{Surekha M.V.}: Analysis and interpretation of haematological and histopathological data; \textbf{Dinesh Kumar B.}: Study design, supervision, and study-director.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have, or could be perceived to have, influenced the work reported in this article.

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