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Methods S1: Full subject inclusion and exclusion criteria

Inclusion criteria:

1. Subjects must meet all of the following criteria to be eligible for enrolment in this study:
2. Subject is a healthy male or female (of non-childbearing potential), aged 18 to 45 years, inclusive.
3. Satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (haematology, biochemistry, coagulation, and urinalysis) that is reasonably likely to interfere with the subject's participation in or ability to complete the study as assessed by the Investigator.
4. Subject has a body weight of at least 50 kg and a body mass index (BMI) of 18–25 kg/m2, inclusive.
5. Female subjects must be of non-childbearing potential:
	1. Natural (spontaneous) post-menopausal defined as being amenorrheic for at least 12 months without an alternative medical cause with a screening follicle stimulating hormone level > 25 IU/L (or at the local laboratory levels for post-menopause).
	2. Premenopausal with irreversible surgical sterilization by hysterectomy and/or bilateral oophorectomy or salpingectomy at least 6 months before screening (as determined by subject medical history).
6. Heterosexually active male subjects with a female spouse/partner of childbearing potential must agree to use barrier contraception (male condom), even with documented medical assessment of surgical success of a vasectomy, if their partner could become pregnant from the time of the first administration of P218 and for 100 days following this. Their partner must also use a method of highly effective contraception.
7. Subjects are non-smokers or ex-smokers for more than 90 days prior to screening or smoke no more than 5 cigarettes per day. If users of nicotine products (i.e. spray, patch, e-cigarette, etc.) they should use the equivalent of no more than 5 cigarettes per day. Subjects must agree to abstain from smoking while in the unit.
8. Ability to swallow multiple capsules at a time or (consecutively) 1 capsule at a time.
9. Subjects must be capable of fully understanding and complying with the requirements of the study and must have signed the informed consent form prior to undergoing any study related procedures.
10. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion criteria:

1. Male subjects of a female partner who was pregnant or lactating were excluded.
2. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means.
3. Evidence or history of clinically significant haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease.
4. Current or relevant history of physical or psychiatric illness that may require treatment or make the subject unlikely to fully comply with the requirements or complete the study, or any condition that presents undue risk from the investigational product or study procedures.
5. Any surgical or medical condition possibly affecting drug absorption, distribution, metabolism or excretion
6. Any history of gallbladder disease, including cholecystitis and/or cholelithiasis
7. Any other significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of the participation in the study may influence the result of the study, or the subject’s ability to participate in the study;
8. History of photosensitivity.
9. History of megaloblastic anaemia or folate deficiency.
10. History or clinical evidence of substance and/or alcohol abuse within the 12 months before screening.
11. Treatment with an investigational drug within 90 days or 5 half-lives preceding the first dose of study medication (or as determined by the local requirement, whichever is the longer).
12. Donation of blood or blood products (excluding plasma) within 90 days prior to study medication administration.
13. Use of moderate/strong inhibitors or inducers of CYP450 cytochromes or transporters within 30 days or 5 half-lives (whichever is the longer) prior to the first dose of study medication.
14. Consumption of grapefruit, grapefruit juice or grapefruit-related citrus fruits (e.g. Seville oranges, pomelos) within 30 days prior to the first dose of study medication.
15. Ingestion of any poppy seeds within the 24 hours prior to screening.
16. Use of prescription or non-prescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is the longer) prior to the first dose of study medication. With the exception of paracetamol, which may be used incidentally or for a short-term treatment at a maximum dose of 1 g per day.
17. Use of herbal supplements at least 30 days prior to the first dose of study medication.
18. Any clinically significant abnormal laboratory, vital signs or other safety findings as determined by medical history, physical examination or other evaluations conducted at screening or on admission.
19. The history or presence of any of the following cardiac conditions: known structural cardiac abnormalities; family history of long QT syndrome; cardiac syncope or recurrent, idiopathic syncope; exercise related clinically significant cardiac events.
	1. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG that may interfere with the interpretation of QTc interval changes. This includes subjects with any of the following (at screening):
		1. Sinus node dysfunction.
		2. Clinically significant PR (PQ) interval prolongation.
		3. Intermittent second or third degree AV block.
		4. Incomplete or complete bundle branch block.
		5. Abnormal T wave morphology.
		6. Prolonged QTcB >450 ms or shortened QTcB <350 ms. Any other ECG abnormalities in the standard 12-lead ECG and 24-hour 12 lead Holter ECG or an equivalent assessment which in the opinion of the Investigator will interfere with the ECG analysis.
	2. Subjects with borderline abnormalities may be included if the deviations do not pose a safety risk, and if agreed between the appointed Cardiologist and the PI.
20. Confirmed positive results from urine drug screen (amphetamines, benzodiazepines, cocaine, cannabinoids, opiates, barbiturates, and methadone) or from the alcohol breath test at screening or on admission.
21. A positive human immunodeficiency virus (HIV) I and II antibodies, hepatitis B surface antigen (HBsAg), anti Hepatitis core antibody (anti HBc Ig G [and anti HBc IgM if IgG is positive], or hepatitis C virus (HCV) antibody at screening.
22. Subjects have veins unsuitable for intravenous puncture or cannulation on either arm (e.g. veins that are difficult to locate access or puncture veins with a tendency to rupture during or after puncture).
23. Any conditions which in the opinion of the investigator would make the subject unsuitable for enrolment or could interfere with the subjects’ participation in or completion of the study.

Table S1: Study safety assessments

|  |  |  |
| --- | --- | --- |
| **Safety assessment** | **Study Parts A & B (periods 1 & 2)** | **Study Part A only** |
| **Screening** | **Day –1** | **Day 1** | **D2** | **D3** | **D4** | **D6** | **D8** | **D9** | **D11** |
| **Pre–dose** | **0 h** | **0.25 h** | **0.5 h** | **1 h** | **2 h** | **4 h** | **8 h** | **12 h** | **24 h** | **48 h** | **72 h** | **120 h** | **168 h** | **192 h** | **240 h** |
| Dosing |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event assessment |  |  |  | X |  |  |  |  |  |  |  |  |  |  | XB |  |  | XA |
| Safety haematology | X | X |  |  |  |  |  |  |  |  |  | X |  | X | XB |  |  | XA |
| Safety biochemistry | X | X |  |  |  |  |  |  |  |  |  | X |  | X | XB |  |  | XA |
| Coagulation | X | X |  |  |  |  |  |  |  |  |  |  |  |  | XB |  |  | XA |
| Urinalysis | X | X | X |  |  |  |  |  |  |  |  | X |  | X | XB |  |  | XA |
| Serum folate levels | X | X |  |  |  |  |  |  |  |  |  | X |  | X | XB |  |  | XA |
| RBC folate levels | X | X |  |  |  |  |  |  |  |  |  | X |  | X | XB |  |  | XA |
| Physical examination | X | X | X |  |  |  |  |  |  |  |  | X |  |  | XB |  |  | XA |
| Vital signs | X | X | X |  |  | X | X | X | X | X | X | X | X | X | X | XA | XA | XA |
| Triplicate 12–lead ECG | X | X | X† |  |  | X | X | X | X | X | X | X | X | X | X | XA | XA | XA |
| TelemetryA |  |  | XA |  |  |  |  |  |  |  | XA |  |  |  |  |  |  |  |
| Concomitant medication | X |  |  |  |  |  |  |  |  |  |  |  |  |  | XB |  |  | XA |

†Triplicate ECGs were conducted at –2, –1 and –0.5 h pre–dose in Part A and –0.5 h pre–dose in Part B.

AOnly done in part A.

BOnly done in Part B.

Table S2: Study pharmacokinetic assessments

|  |  |  |  |
| --- | --- | --- | --- |
| **Study day** | **Time (h)** | **Study Part A** | **Study Part B** |
| **PK blood sampling** | **PK urine sampling†** | **PK blood sampling** |
| D1 | –0.5 | X |  | X |
|  | 0 |  | X |  |
|  | 0.25 | X |  | X |
|  | 0.5 | X |  | X |
|  | 1 | X |  | X |
|  | 2 | X |  | X |
|  | 4 | X |  | X |
|  | 6 | X | X |  |
|  | 7 | X |  |  |
|  | 8 | X |  | X |
|  | 12 | X | X | X |
| D2 | 24 | X | X | X |
| D3 | 48 | X | X | X |
| D4 | 72 | X |  | X |
| D6 | 120 | X |  | X |
| D8 | 168 | X |  |  |
| D9 | 192 | X |  |  |
| D11 | 240 | X |  |  |

†Pooled urine collection at 0–6, 6–12, 12–24 and 24–48 h.

Methods S2: Calculation of P218 concentrations based on an ex vivo antimalarial assay

The exact calculation process of the determination of P218 concentrations based on the *ex* vivo bioassay is described and an example calculation table provided below. Briefly, relying on LC-MS/MS data (provided by Swiss BioQuant) of the parent compound P218, the serum samples were titrated directly into the assay, resulting in a dilution factor of 10x (1 sample), 200x (1 sample) and 4x (4 samples), respectively, (column 3). The experimentally obtained bioassay IC50 values (column 5) were then normalized to 0.43 ng/mL (column 6), a value corresponding to the IC50 obtained with reference serum sample spiked with a known amount of P218, and titrated into the *P. falciparum* assay (data not shown). The ratio between 0.43 ng/mL and the experimentally obtained IC50 for each time point (column 6) was then multiplied with the corresponding LC-MS/MS values (column 2) in order to calculate the concentration of active substance(s) in each serum sample (column 7).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sample number | Time (h) | Concentration determined by LC-MS/MS (ng/mL) | Dilution factor before and/or during addition into bioassay | Highest concentration titrated into bioassay (ng/mL) | IC50 determined by bioassay (ng/mL) | 0.43 ng/mL divided by the IC50 determined in the bioassay (ng/mL) | Concentration determined by bioassay (ng/mL) |
| 1. | 1 | 105 | 10 | 10.5 | 0.22 | 1.95 | 205.23 |
| 2. | 2 | 1850 | 200 | 9.25 | 0.19 | 2.26 | 4186.84 |

Table S3: Mean (SD) values for haematological measures following single doses of P218 or placebo

| **Measure/****Study day** | **Part A** | **Part B** |
| --- | --- | --- |
| **Value** | **10 mg (N=6)** | **30 mg (N=6)** | **100 mg (N=6)** | **250 mg (N=6)** | **500 mg (N=6)** | **750 mg (N=6)** | **1000 mg (N=6)** | **Placebo (N=14)** | **Study day** | **250 mg fasted (N=8)** | **250 mg fed****(N=8)** |
| **Basophils, x109/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 0.023 | 0.023 | 0.027 | 0.027 | 0.028 | 0.040 | 0.043 | 0.030 | –1 | 0.033 | 0.029 |
| SD | 0.008 | 0.005 | 0.015 | 0.018 | 0.019 | 0.014 | 0.023 | 0.015 | 0.021 | 0.016 |
| 2 | Mean | 0.023 | 0.025 | 0.037 | 0.030 | 0.023 | 0.038 | 0.047 | 0.034 | 2 | 0.025 | 0.031 |
| SD | 0.010 | 0.008 | 0.018 | 0.011 | 0.012 | 0.015 | 0.020 | 0.016 | 0.014 | 0.022 |
| 4 | Mean | 0.020 | 0.015 | 0.028 | 0.027 | 0.025 | 0.035 | 0.038 | 0.029 | 4 | 0.028 | 0.031 |
| SD | 0.006 | 0.006 | 0.010 | 0.014 | 0.016 | 0.018 | 0.025 | 0.014 | 0.009 | 0.029 |
| 11 | Mean | 0.023 | 0.018 | 0.028 | 0.024 | 0.025 | 0.035 | 0.042 | 0.029 | 6 | 0.029 | 0.029 |
| SD | 0.008 | 0.008 | 0.013 | 0.015 | 0.015 | 0.011 | 0.026 | 0.013 | 0.017 | 0.022 |
| **Eosinophils, x109/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 0.293 | 0.222 | 0.100 | 0.327 | 0.197 | 0.165 | 0.188 | 0.228 | –1 | 0.084 | 0.090 |
| SD | 0.253 | 0.142 | 0.043 | 0.173 | 0.184 | 0.177 | 0.171 | 0.121 | 0.087 | 0.081 |
| 2 | Mean | 0.283 | 0.257 | 0.118 | 0.318 | 0.213 | 0.178 | 0.240 | 0.250 | 2 | 0.104 | 0.110 |
| SD | 0.196 | 0.168 | 0.050 | 0.176 | 0.155 | 0.118 | 0.204 | 0.114 | 0.077 | 0.082 |
| 4 | Mean | 0.233 | 0.207 | 0.140 | 0.318 | 0.252 | 0.173 | 0.240 | 0.239 | 4 | 0.108 | 0.119 |
| SD | 0.177 | 0.133 | 0.065 | 0.187 | 0.185 | 0.117 | 0.245 | 0.096 | 0.075 | 0.104 |
| 11 | Mean | 0.218 | 0.240 | 0.122 | 0.360 | 0.195 | 0.152 | 0.212 | 0.232 | 6 | 0.140 | 0.095 |
| SD | 0.154 | 0.213 | 0.043 | 0.366 | 0.162 | 0.103 | 0.197 | 0.112 | 0.139 | 0.094 |
| **Erythrocytes, x1012/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 4.96 | 5.17 | 5.20 | 4.97 | 5.12 | 4.83 | 5.34 | 5.14 | –1 | 4.90 | 4.89 |
| SD | 0.31 | 0.66 | 0.30 | 0.41 | 0.32 | 0.37 | 0.28 | 0.45 | 0.46 | 0.60 |
| 2 | Mean | 5.16 | 5.36 | 5.21 | 5.21 | 5.14 | 5.29 | 5.55 | 5.31 | 2 | 4.99 | 5.02 |
| SD | 0.27 | 0.52 | 0.18 | 0.30 | 0.37 | 0.62 | 0.29 | 0.41 | 0.46 | 0.50 |
| 4 | Mean | 5.09 | 5.20 | 5.07 | 5.00 | 5.13 | 5.24 | 5.16 | 5.21 | 4 | 5.01 | 5.11 |
| SD | 0.27 | 0.52 | 0.24 | 0.32 | 0.44 | 0.56 | 0.24 | 0.43 | 0.49 | 0.47 |
| 11 | Mean | 4.96 | 4.85 | 5.01 | 4.87 | 4.79 | 4.84 | 5.07 | 5.03 | 6 | 4.79 | 4.80 |
| SD | 0.28 | 0.43 | 0.23 | 0.18 | 0.39 | 0.55 | 0.25 | 0.38 | 0.40 | 0.48 |
| **Haematocrit, %** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 42.6 | 43.7 | 44.8 | 43.6 | 43.9 | 42.9 | 47.1 | 43.6 | –1 | 44.0 | 43.7 |
| SD | 1.9 | 4.0 | 2.3 | 3.6 | 3.1 | 2.4 | 2.2 | 3.5 | 3.0 | 3.5 |
| 2 | Mean | 44.1 | 45.4 | 45.5 | 45.9 | 44.0 | 46.7 | 48.6 | 45.2 | 2 | 44.7 | 45.1 |
| SD | 2.0 | 3.3 | 1.6 | 2.0 | 2.6 | 4.0 | 2.3 | 3.0 | 2.8 | 3.1 |
| 4 | Mean | 43.9 | 44.0 | 44.3 | 43.2 | 43.5 | 47.0 | 45.0 | 44.2 | 4 | 44.9 | 45.7 |
| SD | 1.5 | 2.9 | 2.5 | 2.1 | 2.4 | 3.5 | 2.4 | 3.0 | 3.3 | 3.3 |
| 11 | Mean | 42.7 | 41.2 | 43.4 | 42.9 | 40.9 | 45.0 | 44.2 | 43.0 | 6 | 43.2 | 43.2 |
| SD | 1.9 | 2.3 | 1.7 | 1.5 | 1.8 | 3.9 | 1.7 | 2.6 | 2.0 | 2.2 |
| **Haematocrit, /L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 0.426 | 0.437 | 0.448 | 0.436 | 0.439 | 0.429 | – | 0.431 | –1 | – | – |
| SD | 0.019 | 0.040 | 0.023 | 0.036 | 0.031 | 0.024 | – | 0.029 | – | – |
| 2 | Mean | 0.441 | 0.454 | 0.455 | 0.459 | 0.440 | 0.467 | – | 0.446 | 2 | – | – |
| SD | 0.020 | 0.033 | 0.016 | 0.020 | 0.026 | 0.040 | – | 0.029 | – | – |
| 4 | Mean | 0.439 | 0.440 | 0.443 | 0.432 | 0.435 | 0.470 | – | 0.438 | 4 | – | – |
| SD | 0.015 | 0.029 | 0.025 | 0.021 | 0.024 | 0.035 | – | 0.030 | – | – |
| 11 | Mean | 0.427 | 0.412 | 0.434 | 0.429 | 0.409 | 0.450 | – | 0.430 | 6 | – | – |
| SD | 0.020 | 0.023 | 0.017 | 0.015 | 0.018 | 0.039 | – | 0.028 | – | – |
| **Haemoglobin, g/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 147.3 | 152.0 | 152.2 | 146.3 | 146.3 | 148.0 | 155.8 | 148.9 | –1 | 146.5 | 145.6 |
| SD | 7.9 | 10.5 | 9.8 | 10.7 | 13.6 | 7.9 | 4.9 | 12.3 | 8.9 | 11.0 |
| 2 | Mean | 153.2 | 157.0 | 154.2 | 155.2 | 148.3 | 163.7 | 161.7 | 153.9 | 2 | 150.4 | 150.8 |
| SD | 8.1 | 9.8 | 7.9 | 7.4 | 11.9 | 12.0 | 6.2 | 10.6 | 7.8 | 10.2 |
| 4 | Mean | 152.2 | 152.0 | 149.2 | 149.5 | 145.7 | 161.7 | 154.7 | 151.1 | 4 | 152.0 | 154.9 |
| SD | 6.9 | 9.2 | 10.2 | 6.7 | 8.2 | 10.6 | 6.2 | 11.2 | 9.0 | 10.1 |
| 11 | Mean | 147.7 | 141.7 | 146.8 | 143.6 | 135.8 | 150.3 | 152.7 | 146.1 | 6 | 144.6 | 144.9 |
| SD | 7.6 | 8.9 | 7.6 | 4.5 | 8.2 | 10.0 | 5.5 | 11.2 | 7.3 | 9.2 |
| **Lymphocytes, x109/L** |  |   |   |   |   |   |   |   |   |  |  |  |
|  | Mean | 1.81 | 2.05 | 1.71 | 1.74 | 1.96 | 1.51 | 1.76 | 1.84 | –1 | 1.72 | 1.92 |
| SD | 0.21 | 0.61 | 0.30 | 0.32 | 0.53 | 0.49 | 0.41 | 0.38 | 0.66 | 0.60 |
| 2 | Mean | 1.83 | 2.29 | 1.81 | 1.89 | 2.19 | 1.83 | 2.07 | 2.18 | 2 | 1.71 | 1.82 |
| SD | 0.21 | 0.53 | 0.26 | 0.35 | 0.58 | 0.36 | 0.41 | 0.50 | 0.51 | 0.48 |
| 4 | Mean | 1.57 | 1.88 | 1.73 | 1.77 | 2.02 | 1.65 | 1.98 | 1.92 | 4 | 1.77 | 1.78 |
| SD | 0.21 | 0.45 | 0.58 | 0.31 | 0.42 | 0.17 | 0.39 | 0.42 | 0.48 | 0.44 |
| 11 | Mean | 1.63 | 1.85 | 1.53 | 1.54 | 2.01 | 1.47 | 1.48 | 1.82 | 6 | 1.68 | 1.74 |
| SD | 0.50 | 0.38 | 0.31 | 0.43 | 0.46 | 0.28 | 0.11 | 0.35 | 0.54 | 0.49 |
| **Mean cell haemoglobin, pg** |  |   |   |   |   |   |   |   |  |  |  |  |
| –1 | Mean | 29.8 | 29.6 | 29.3 | 29.5 | 28.7 | 30.7 | 29.2 | 29.0 | –1 | 30.0 | 30.0 |
| SD | 1.1 | 2.1 | 1.4 | 1.0 | 2.6 | 1.3 | 0.7 | 1.8 | 1.7 | 1.7 |
| 2 | Mean | 29.7 | 29.4 | 29.6 | 29.9 | 28.9 | 31.1 | 29.2 | 29.1 | 2 | 30.3 | 30.1 |
| SD | 0.9 | 1.7 | 1.2 | 1.1 | 2.7 | 1.4 | 0.7 | 1.9 | 1.9 | 1.6 |
| 4 | Mean | 29.9 | 29.4 | 29.4 | 30.0 | 28.5 | 31.0 | 30.0 | 29.1 | 4 | 30.5 | 30.4 |
| SD | 1.1 | 2.0 | 1.3 | 1.1 | 2.5 | 1.5 | 0.6 | 2.1 | 1.7 | 1.4 |
| 11 | Mean | 29.8 | 29.3 | 29.3 | 29.5 | 28.5 | 31.2 | 30.2 | 29.1 | 6 | 30.3 | 30.3 |
| SD | 0.9 | 2.0 | 1.4 | 0.8 | 2.4 | 1.9 | 0.9 | 2.1 | 1.8 | 1.5 |
| **Mean corpuscular volume, fl** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 86.1 | 84.7 | 86.3 | 87.8 | 85.9 | 88.8 | 88.3 | 85.0 | –1 | 90.2 | 90.0 |
| SD | 3.2 | 3.8 | 2.7 | 2.9 | 6.2 | 3.3 | 3.3 | 4.8 | 5.4 | 5.6 |
| 2 | Mean | 85.4 | 84.9 | 87.3 | 88.3 | 85.7 | 88.4 | 87.7 | 85.2 | 2 | 90.0 | 90.0 |
| SD | 2.3 | 3.9 | 2.3 | 3.1 | 5.6 | 3.4 | 2.9 | 4.8 | 5.2 | 5.1 |
| 4 | Mean | 86.3 | 84.9 | 87.3 | 86.6 | 85.1 | 89.9 | 87.2 | 85.1 | 4 | 90.0 | 89.7 |
| SD | 2.6 | 4.0 | 2.4 | 2.8 | 6.0 | 3.3 | 3.2 | 4.8 | 5.1 | 5.4 |
| 11 | Mean | 86.0 | 85.4 | 86.8 | 88.1 | 85.8 | 93.7 | 87.2 | 85.7 | 6 | 90.5 | 90.4 |
| SD | 2.4 | 4.4 | 2.7 | 2.6 | 5.7 | 9.7 | 2.9 | 5.2 | 5.3 | 5.3 |
| **Mean corpuscular haemoglobin concentration, g/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 345.7 | 348.7 | 339.5 | 335.5 | 333.3 | 345.5 | 331.3 | 341.1 | –1 | 332.9 | 333.4 |
| SD | 6.0 | 13.1 | 6.7 | 4.1 | 7.4 | 9.1 | 11.1 | 8.1 | 8.4 | 9.6 |
| 2 | Mean | 347.7 | 346.2 | 339.0 | 337.8 | 337.0 | 351.0 | 332.8 | 340.7 | 2 | 336.6 | 334.6 |
| SD | 5.1 | 7.7 | 6.9 | 4.8 | 10.0 | 5.5 | 6.4 | 9.5 | 7.1 | 8.0 |
| 4 | Mean | 346.5 | 345.8 | 336.7 | 346.2 | 334.7 | 344.5 | 344.2 | 341.5 | 4 | 338.5 | 339.1 |
| SD | 8.0 | 8.1 | 6.4 | 5.2 | 7.2 | 7.9 | 11.0 | 9.7 | 7.8 | 8.1 |
| 11 | Mean | 346.0 | 343.7 | 338.0 | 335.0 | 331.8 | 335.2 | 346.0 | 339.4 | 6 | 334.7 | 335.5 |
| SD | 8.2 | 9.8 | 7.5 | 2.5 | 9.7 | 24.4 | 5.3 | 12.3 | 6.6 | 9.5 |
| **Monocytes, x109/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 0.453 | 0.450 | 0.465 | 0.560 | 0.723 | 0.525 | 0.490 | 0.496 | –1 | 0.543 | 0.521 |
| SD | 0.074 | 0.087 | 0.117 | 0.158 | 0.466 | 0.090 | 0.139 | 0.137 | 0.249 | 0.162 |
| 2 | Mean | 0.517 | 0.497 | 0.475 | 0.622 | 0.723 | 0.638 | 0.632 | 0.553 | 2 | 0.488 | 0.484 |
| SD | 0.223 | 0.081 | 0.120 | 0.117 | 0.637 | 0.144 | 0.136 | 0.142 | 0.159 | 0.175 |
| 4 | Mean | 0.455 | 0.415 | 0.507 | 0.558 | 0.558 | 0.500 | 0.620 | 0.511 | 4 | 0.425 | 0.469 |
| SD | 0.162 | 0.107 | 0.153 | 0.120 | 0.178 | 0.064 | 0.165 | 0.143 | 0.139 | 0.233 |
| 11 | Mean | 0.460 | 0.538 | 0.475 | 0.574 | 0.518 | 0.483 | 0.525 | 0.444 | 6 | 0.480 | 0.460 |
| SD | 0.119 | 0.147 | 0.101 | 0.252 | 0.153 | 0.051 | 0.176 | 0.119 | 0.206 | 0.258 |
| **Neutrophils, x109/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 2.70 | 2.70 | 2.86 | 2.75 | 4.00 | 3.60 | 2.80 | 3.00 | –1 | 3.45 | 3.06 |
| SD | 0.50 | 0.60 | 1.03 | 0.65 | 2.20 | 0.80 | 0.70 | 1.30 | 1.29 | 1.13 |
| 2 | Mean | 3.29 | 3.23 | 2.75 | 3.27 | 3.50 | 3.70 | 3.10 | 3.00 | 2 | 2.90 | 2.68 |
| SD | 0.52 | 0.69 | 0.90 | 0.44 | 1.60 | 1.50 | 0.70 | 1.50 | 1.02 | 0.93 |
| 4 | Mean | 2.80 | 2.57 | 2.88 | 2.64 | 2.64 | 3.13 | 3.21 | 2.87 | 4 | 2.71 | 2.80 |
| SD | 0.38 | 0.75 | 1.35 | 0.67 | 0.52 | 0.51 | 1.42 | 1.20 | 1.06 | 1.01 |
| 11 | Mean | 2.72 | 3.22 | 2.81 | 4.36 | 2.94 | 3.45 | 2.98 | 2.69 | 6 | 2.63 | 2.69 |
| SD | 0.64 | 0.94 | 0.83 | 2.69 | 0.76 | 1.38 | 1.12 | 0.70 | 0.62 | 1.12 |
| **Platelets, x109/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 224.3 | 220.7 | 247.8 | 223.5 | 196.8 | 205.0 | 228.7 | 223.0 | –1 | 216.6 | 213.3 |
| SD | 28.8 | 26.9 | 44.0 | 30.2 | 33.4 | 27.3 | 45.8 | 44.7 | 33.5 | 23.7 |
| 2 | Mean | 236.5 | 225.2 | 235.8 | 243.0 | 181.7 | 216.7 | 227.0 | 221.5 | 2 | 204.8 | 208.5 |
| SD | 21.1 | 22.4 | 38.8 | 37.2 | 34.9 | 36.7 | 44.5 | 45.0 | 31.0 | 26.7 |
| 4 | Mean | 220.7 | 195.7 | 231.0 | 229.5 | 178.8 | 218.0 | 221.5 | 208.7 | 4 | 217.6 | 212.6 |
| SD | 24.1 | 46.3 | 32.5 | 35.4 | 24.5 | 40.9 | 42.5 | 37.5 | 24.1 | 28.5 |
| 11 | Mean | 238.5 | 218.2 | 241.7 | 233.8 | 198.5 | 225.7 | 217.5 | 223.6 | 6 | 222.3 | 209.3 |
| SD | 22.3 | 36.4 | 48.0 | 38.7 | 49.7 | 37.7 | 43.3 | 39.7 | 22.7 | 32.7 |
| **Reticulocytes absolute, x109/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 46.0 | 41.9 | 43.3 | 48.7 | 39.4 | 40.7 | 60.1 | 49.7 | –1 | 72.7 | 69.1 |
| SD | 9.7 | 11.0 | 11.1 | 19.3 | 12.9 | 13.0 | 20.2 | 21.0 | 27.2 | 31.0 |
| 2 | Mean | 47.5 | 46.1 | 40.7 | 52.9 | 35.9 | 46.0 | 63.2 | 50.1 | 2 | 72.0 | 74.4 |
| SD | 11.0 | 8.0 | 9.7 | 15.8 | 9.0 | 18.5 | 13.9 | 20.0 | 34.7 | 31.7 |
| 4 | Mean | 49.7 | 44.7 | 39.8 | 49.5 | 36.9 | 39.1 | 54.7 | 49.3 | 4 | 75.5 | 79.7 |
| SD | 9.9 | 10.1 | 6.5 | 16.0 | 7.3 | 9.8 | 13.2 | 20.3 | 33.0 | 31.8 |
| 11 | Mean | 50.0 | 48.3 | 41.9 | 54.4 | 39.8 | 45.4 | 58.8 | 48.6 | 6 | 63.6 | 75.9 |
| SD | 9.4 | 8.5 | 11.3 | 11.8 | 10.6 | 16.0 | 15.1 | 14.3 | 17.3 | 23.2 |
| **Reticulocytes, %** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 0.900 | 0.812 | 0.833 | 0.965 | 0.770 | 0.837 | 1.118 | 0.966 | –1 | 1.483 | 1.439 |
| SD | 0.200 | 0.198 | 0.198 | 0.341 | 0.256 | 0.242 | 0.338 | 0.376 | 0.538 | 0.697 |
| 2 | Mean | 0.922 | 0.863 | 0.785 | 1.008 | 0.693 | 0.855 | 1.142 | 0.948 | 2 | 1.439 | 1.485 |
| SD | 0.213 | 0.155 | 0.193 | 0.280 | 0.166 | 0.290 | 0.260 | 0.372 | 0.663 | 0.628 |
| 4 | Mean | 0.982 | 0.863 | 0.785 | 0.980 | 0.715 | 0.745 | 1.067 | 0.947 | 4 | 1.499 | 1.564 |
| SD | 0.215 | 0.196 | 0.123 | 0.276 | 0.107 | 0.164 | 0.278 | 0.377 | 0.622 | 0.597 |
| 11 | Mean | 1.010 | 1.005 | 0.835 | 1.116 | 0.835 | 0.928 | 1.160 | 0.970 | 6 | 1.329 | 1.595 |
| SD | 0.191 | 0.210 | 0.202 | 0.234 | 0.251 | 0.262 | 0.284 | 0.280 | 0.360 | 0.543 |
| **White blood cell count, x109/L** |  |   |   |   |   |   |   |   |   |  |  |  |
| –1 | Mean | 5.30 | 5.47 | 5.17 | 5.40 | 6.93 | 5.85 | 5.28 | 5.63 | –1 | 5.83 | 5.62 |
| SD | 0.40 | 0.84 | 1.30 | 0.58 | 2.40 | 1.27 | 1.21 | 1.49 | 1.75 | 1.37 |
| 2 | Mean | 5.94 | 6.30 | 5.19 | 6.14 | 6.60 | 6.35 | 6.13 | 6.04 | 2 | 5.23 | 5.12 |
| SD | 0.59 | 0.91 | 1.05 | 0.51 | 2.53 | 1.71 | 1.09 | 1.68 | 1.10 | 1.18 |
| 4 | Mean | 5.07 | 5.09 | 5.28 | 5.31 | 5.49 | 5.49 | 6.09 | 5.57 | 4 | 5.04 | 5.21 |
| SD | 0.35 | 0.99 | 1.35 | 0.83 | 1.01 | 0.54 | 1.67 | 1.22 | 1.39 | 1.26 |
| 11 | Mean | 5.05 | 5.86 | 4.96 | 6.86 | 5.68 | 5.59 | 5.24 | 5.22 | 6 | 4.96 | 5.01 |
| SD | 0.69 | 1.03 | 0.94 | 2.71 | 1.00 | 1.65 | 1.51 | 1.00 | 1.29 | 1.44 |

Table S4: Mean (SD) values for laboratory measures following single doses of P218 or placebo

| **Measure/****Study day** | **Part A** | **Part B** |
| --- | --- | --- |
| **Value** | **10 mg (N=6)** | **30 mg (N=6)** | **100 mg (N=6)** | **250 mg (N=6)** | **500 mg (N=6)** | **750 mg (N=6)** | **1000 mg (N=6)** | **Placebo (N=14)** | **Study day** | **250 mg fasted (N=8)** | **250 mg fed****(N=8)** |
| **Alanine aminotransferase, IU/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 21.83 | 24.33 | 20.50 | 22.50 | 19.33 | 22.33 | 26.83 | 19.93 | –1 | 23.88 | 23.38 |
| SD | 9.45 | 12.32 | 4.32 | 8.83 | 3.62 | 7.12 | 10.42 | 6.91 | 5.87 | 8.63 |
| 2 | Mean | 22.67 | 28.67 | 23.33 | 23.50 | 20.17 | 23.33 | 31.17 | 20.43 | 2 | 21.63 | 22.63 |
| SD | 10.86 | 18.00 | 7.31 | 9.61 | 7.91 | 10.35 | 15.87 | 6.17 | 5.07 | 7.52 |
| 4 | Mean | 22.00 | 26.33 | 21.67 | 23.00 | 18.00 | 24.67 | 30.83 | 19.93 | 4 | 22.50 | 24.50 |
| SD | 9.63 | 19.22 | 8.07 | 8.00 | 6.78 | 11.99 | 15.41 | 5.60 | 8.75 | 11.23 |
| 11 | Mean | 20.83 | 23.83 | 18.50 | 24.17 | 16.67 | 21.00 | 29.17 | 19.21 | 6 | 25.50 | 27.88 |
| SD | 8.95 | 10.72 | 5.61 | 13.09 | 3.01 | 14.28 | 13.66 | 6.29 | 8.38 | 12.78 |
| **Albumin, g/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 45.17 | 46.50 | 46.00 | 46.50 | 48.83 | 44.83 | 46.83 | 46.64 | –1 | 47.50 | 47.13 |
| SD | 2.99 | 2.67 | 2.61 | 2.88 | 1.84 | 1.47 | 1.47 | 2.24 | 2.98 | 2.90 |
| 2 | Mean | 45.83 | 47.33 | 47.67 | 48.50 | 46.50 | 46.83 | 47.17 | 46.64 | 2 | 45.50 | 45.88 |
| SD | 2.86 | 3.72 | 1.97 | 1.87 | 2.74 | 3.19 | 4.36 | 2.21 | 2.07 | 2.70 |
| 4 | Mean | 45.00 | 45.67 | 45.33 | 45.50 | 45.83 | 46.17 | 45.17 | 45.57 | 4 | 47.13 | 47.75 |
| SD | 3.41 | 4.32 | 2.07 | 0.55 | 2.32 | 1.33 | 3.37 | 2.17 | 2.17 | 4.13 |
| 11 | Mean | 46.33 | 44.67 | 46.50 | 46.17 | 45.50 | 44.83 | 46.33 | 46.29 | 6 | 46.75 | 47.38 |
| SD | 2.94 | 2.16 | 1.52 | 2.04 | 2.81 | 1.72 | 3.01 | 2.40 | 3.92 | 2.56 |
| **Alkaline phosphatase, IU/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 65.67 | 73.17 | 56.83 | 74.83 | 64.83 | 63.67 | 67.83 | 63.43 | –1 | 68.50 | 64.88 |
| SD | 12.16 | 23.22 | 16.33 | 26.51 | 6.11 | 5.99 | 10.07 | 16.43 | 25.95 | 24.96 |
| 2 | Mean | 66.33 | 74.83 | 59.67 | 82.33 | 65.83 | 69.00 | 68.33 | 65.36 | 2 | 65.50 | 63.50 |
| SD | 12.94 | 22.90 | 13.16 | 25.24 | 7.47 | 7.54 | 13.17 | 17.09 | 23.79 | 23.67 |
| 4 | Mean | 64.50 | 71.83 | 55.50 | 75.50 | 65.67 | 64.33 | 61.00 | 63.00 | 4 | 66.13 | 65.38 |
| SD | 11.43 | 22.83 | 13.74 | 23.58 | 7.34 | 8.50 | 12.67 | 14.38 | 23.03 | 23.00 |
| 11 | Mean | 65.50 | 70.33 | 63.83 | 72.67 | 62.67 | 60.83 | 65.83 | 63.93 | 6 | 68.25 | 66.25 |
| SD | 12.44 | 21.00 | 14.58 | 22.66 | 6.28 | 8.52 | 13.60 | 15.51 | 23.22 | 23.91 |
| **Aspartate transaminase, IU/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 20.33 | 20.83 | 18.83 | 20.17 | 19.67 | 17.83 | 23.67 | 22.00 | –1 | 24.25 | 23.13 |
| SD | 3.56 | 4.62 | 3.06 | 4.07 | 4.08 | 3.13 | 3.20 | 5.55 | 3.73 | 4.49 |
| 2 | Mean | 19.67 | 19.33 | 18.33 | 20.50 | 19.00 | 19.17 | 23.67 | 19.93 | 2 | 17.50 | 19.00 |
| SD | 3.14 | 7.01 | 4.84 | 5.75 | 4.29 | 5.00 | 6.15 | 3.91 | 3.34 | 4.66 |
| 4 | Mean | 19.17 | 18.00 | 16.67 | 19.17 | 16.50 | 19.17 | 21.50 | 19.29 | 4 | 20.38 | 20.00 |
| SD | 2.48 | 5.14 | 4.63 | 4.49 | 2.88 | 3.92 | 4.72 | 3.89 | 4.44 | 4.32 |
| 11 | Mean | 20.33 | 17.00 | 18.67 | 21.00 | 17.83 | 18.33 | 21.67 | 20.29 | 6 | 25.13 | 25.88 |
| SD | 3.39 | 4.78 | 2.73 | 4.94 | 4.17 | 6.44 | 3.20 | 4.12 | 5.52 | 8.03 |
| **Blood urea nitrogen, mg/dL** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 15.31 | 14.28 | 12.88 | 15.26 | 14.37 | 14.23 | 14.61 | 14.78 | –1 | 14.53 | 14.88 |
| SD | 3.34 | 2.06 | 2.63 | 6.81 | 3.80 | 2.65 | 3.24 | 2.84 | 3.50 | 3.33 |
| 2 | Mean | 12.18 | 13.21 | 11.99 | 13.07 | 12.09 | 14.65 | 14.19 | 13.00 | 2 | 12.04 | 13.02 |
| SD | 2.30 | 1.41 | 2.90 | 3.68 | 1.94 | 2.01 | 1.74 | 2.12 | 2.35 | 2.16 |
| 4 | Mean | 11.71 | 12.04 | 12.18 | 13.11 | 12.37 | 14.00 | 14.93 | 11.92 | 4 | 13.09 | 14.04 |
| SD | 2.87 | 1.03 | 2.84 | 3.39 | 2.18 | 1.60 | 2.31 | 2.22 | 2.37 | 1.64 |
| 11 | Mean | 14.23 | 12.04 | 12.04 | 14.33 | 11.48 | 13.91 | 15.68 | 13.38 | 6 | 12.81 | 13.06 |
| SD | 3.97 | 3.00 | 2.67 | 4.45 | 2.39 | 3.37 | 2.84 | 3.53 | 3.23 | 3.24 |
| **C-reactive protein, mg/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 0.98 | 0.65 | 1.27 | 1.62 | 1.45 | 1.80 | 2.60 | 0.81 | –1 | 0.95 | 0.65 |
| SD | 0.76 | 0.12 | 1.04 | 1.98 | 1.70 | 2.36 | 3.91 | 0.46 | 0.67 | 0.11 |
| 2 | Mean | 1.40 | 0.73 | 0.85 | 1.28 | 4.43 | 1.78 | 1.23 | 0.86 | 2 | 1.36 | 0.69 |
| SD | 1.54 | 0.33 | 0.40 | 1.36 | 9.15 | 2.05 | 0.95 | 0.85 | 2.16 | 0.25 |
| 4 | Mean | 0.88 | 0.73 | 0.70 | 0.88 | 2.67 | 1.17 | 0.72 | 1.06 | 4 | 0.71 | 0.60 |
| SD | 0.65 | 0.33 | 0.25 | 0.65 | 5.06 | 1.16 | 0.20 | 1.74 | 0.32 | 0.00 |
| 11 | Mean | 0.70 | 1.18 | 1.08 | 1.02 | 2.40 | 0.93 | 0.75 | 0.71 | 6 | 1.05 | 0.60 |
| SD | 0.17 | 0.88 | 0.83 | 0.67 | 4.17 | 0.45 | 0.37 | 0.24 | 1.02 | 0.00 |
| **Calcium, mmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 2.38 | 2.48 | 2.44 | 2.42 | 2.46 | 2.34 | 2.47 | 2.41 | –1 | 2.43 | 2.44 |
| SD | 0.08 | 0.07 | 0.11 | 0.14 | 0.09 | 0.07 | 0.11 | 0.07 | 0.07 | 0.08 |
| 2 | Mean | 2.41 | 2.49 | 2.51 | 2.47 | 2.43 | 2.47 | 2.49 | 2.46 | 2 | 2.42 | 2.41 |
| SD | 0.09 | 0.12 | 0.08 | 0.08 | 0.12 | 0.09 | 0.11 | 0.09 | 0.07 | 0.05 |
| 4 | Mean | 2.48 | 2.44 | 2.42 | 2.46 | 2.49 | 2.47 | 2.46 | 2.45 | 4 | 2.45 | 2.45 |
| SD | 0.11 | 0.13 | 0.10 | 0.10 | 0.09 | 0.06 | 0.12 | 0.09 | 0.07 | 0.08 |
| 11 | Mean | 2.45 | 2.39 | 2.47 | 2.40 | 2.41 | 2.40 | 2.43 | 2.44 | 6 | 2.39 | 2.43 |
| SD | 0.08 | 0.07 | 0.10 | 0.07 | 0.08 | 0.10 | 0.09 | 0.07 | 0.08 | 0.05 |
| **Chloride, mmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 103.00 | 101.00 | 100.67 | 101.33 | 101.00 | 101.33 | 99.50 | 101.43 | –1 | 100.38 | 101.25 |
| SD | 1.67 | 2.00 | 1.37 | 0.52 | 1.10 | 2.88 | 1.23 | 1.51 | 0.52 | 1.75 |
| 2 | Mean | 100.67 | 99.33 | 101.17 | 100.00 | 98.83 | 99.83 | 97.83 | 100.14 | 2 | 99.50 | 100.25 |
| SD | 2.25 | 2.34 | 1.17 | 2.10 | 1.17 | 1.94 | 1.33 | 1.23 | 1.60 | 1.58 |
| 4 | Mean | 101.50 | 100.17 | 101.50 | 101.83 | 100.67 | 100.83 | 100.50 | 101.64 | 4 | 101.25 | 100.75 |
| SD | 1.52 | 1.94 | 0.84 | 1.60 | 1.03 | 2.04 | 1.05 | 2.10 | 1.75 | 1.04 |
| 11 | Mean | 101.33 | 101.33 | 101.17 | 99.17 | 101.50 | 101.00 | 100.17 | 101.50 | 6 | 101.25 | 100.88 |
| SD | 1.86 | 1.03 | 1.47 | 2.14 | 2.59 | 1.79 | 0.98 | 1.83 | 1.49 | 1.64 |
| **Creatine phosphokinase, IU/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 94.17 | 183.00 | 98.33 | 169.83 | 191.33 | 92.00 | 169.67 | 186.07 | –1 | 200.50 | 204.00 |
| SD | 15.88 | 124.71 | 20.44 | 97.92 | 109.13 | 27.41 | 47.04 | 98.67 | 128.17 | 157.36 |
| 2 | Mean | 70.33 | 92.50 | 72.17 | 112.83 | 112.00 | 61.50 | 103.17 | 105.00 | 2 | 107.13 | 141.63 |
| SD | 18.64 | 25.57 | 22.61 | 70.61 | 48.60 | 19.56 | 31.68 | 46.18 | 66.41 | 136.73 |
| 4 | Mean | 64.00 | 81.83 | 63.00 | 110.00 | 92.17 | 59.33 | 88.00 | 98.21 | 4 | 89.50 | 118.86 |
| SD | 15.79 | 21.52 | 25.01 | 88.63 | 38.38 | 16.60 | 26.45 | 60.52 | 47.32 | 72.48 |
| 11 | Mean | 110.83 | 147.33 | 105.50 | 164.17 | 168.00 | 87.50 | 139.83 | 161.00 | 6 | 212.25 | 253.63 |
| SD | 36.04 | 87.30 | 26.91 | 108.48 | 91.33 | 16.60 | 42.60 | 96.67 | 174.44 | 246.31 |
| **Creatinine, µmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 76.17 | 86.83 | 82.67 | 85.83 | 87.67 | 78.50 | 81.50 | 86.43 | –1 | 78.13 | 82.13 |
| SD | 7.17 | 15.45 | 9.75 | 12.67 | 7.71 | 17.21 | 13.10 | 14.60 | 5.57 | 6.13 |
| 2 | Mean | 79.00 | 94.33 | 84.67 | 90.50 | 93.50 | 84.67 | 79.33 | 89.50 | 2 | 84.00 | 81.13 |
| SD | 8.08 | 14.72 | 9.95 | 13.61 | 14.88 | 14.12 | 10.41 | 13.17 | 6.61 | 6.94 |
| 4 | Mean | 78.83 | 92.33 | 78.83 | 88.50 | 92.00 | 79.67 | 88.50 | 89.57 | 4 | 87.38 | 89.00 |
| SD | 7.55 | 11.71 | 5.38 | 13.66 | 10.10 | 13.59 | 9.92 | 12.92 | 8.91 | 8.94 |
| 11 | Mean | 81.17 | 88.17 | 79.00 | 82.00 | 83.83 | 77.17 | 83.33 | 86.57 | 6 | 82.50 | 80.88 |
| SD | 6.34 | 14.18 | 4.29 | 10.28 | 8.70 | 10.11 | 12.74 | 12.33 | 8.94 | 7.28 |
| **Direct bilirubin, µmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 4.17 | 3.83 | 3.67 | 3.00 | 4.33 | 3.33 | 4.50 | 3.50 | –1 | 4.88 | 4.25 |
| SD | 1.60 | 0.98 | 0.52 | 0.63 | 1.37 | 0.82 | 1.05 | 1.29 | 1.64 | 2.19 |
| 2 | Mean | 4.83 | 4.67 | 4.83 | 4.50 | 4.00 | 5.33 | 5.17 | 4.64 | 2 | 5.00 | 5.13 |
| SD | 0.75 | 1.37 | 0.98 | 1.52 | 1.41 | 1.51 | 1.17 | 1.08 | 1.69 | 1.96 |
| 4 | Mean | 4.50 | 4.00 | 4.33 | 3.50 | 4.00 | 4.00 | 4.17 | 3.79 | 4 | 4.50 | 4.88 |
| SD | 0.84 | 0.63 | 1.21 | 1.05 | 0.89 | 0.63 | 0.75 | 1.05 | 1.20 | 1.73 |
| 11 | Mean | 5.00 | 2.83 | 3.33 | 3.17 | 3.17 | 4.50 | 3.50 | 3.36 | 6 | 4.13 | 5.00 |
| SD | 2.45 | 0.75 | 1.51 | 1.17 | 1.47 | 0.55 | 1.05 | 1.28 | 1.89 | 1.85 |
| **Gamma-gt, IU/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 21.67 | 19.17 | 15.83 | 21.50 | 17.00 | 20.83 | 24.17 | 18.79 | –1 | 24.63 | 19.88 |
| SD | 9.27 | 9.20 | 4.67 | 10.82 | 4.05 | 19.77 | 14.33 | 9.55 | 24.24 | 11.43 |
| 2 | Mean | 21.17 | 20.33 | 16.83 | 22.17 | 16.00 | 21.83 | 23.67 | 18.36 | 2 | 22.88 | 19.63 |
| SD | 9.56 | 9.09 | 5.04 | 10.52 | 3.85 | 18.43 | 12.37 | 9.09 | 20.70 | 10.80 |
| 4 | Mean | 21.50 | 19.83 | 16.83 | 20.67 | 15.17 | 20.83 | 21.17 | 17.79 | 4 | 22.88 | 20.13 |
| SD | 11.79 | 9.58 | 4.17 | 8.62 | 3.19 | 18.32 | 10.96 | 8.42 | 20.07 | 10.84 |
| 11 | Mean | 21.67 | 18.17 | 15.50 | 18.83 | 14.67 | 21.17 | 20.83 | 17.50 | 6 | 21.50 | 18.88 |
| SD | 10.99 | 7.83 | 5.24 | 8.04 | 3.01 | 22.03 | 8.68 | 8.10 | 16.47 | 9.37 |
| **Globulin, g/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 22.00 | 23.83 | 24.50 | 21.83 | 26.33 | 21.33 | 23.17 | 24.57 | –1 | 23.50 | 23.38 |
| SD | 3.41 | 3.25 | 4.23 | 3.25 | 4.46 | 3.01 | 2.14 | 4.18 | 3.89 | 4.00 |
| 2 | Mean | 22.50 | 25.67 | 24.00 | 24.83 | 25.67 | 27.33 | 23.67 | 25.14 | 2 | 23.75 | 23.75 |
| SD | 4.23 | 3.88 | 3.63 | 3.31 | 3.62 | 3.33 | 1.75 | 4.07 | 4.71 | 4.13 |
| 4 | Mean | 23.67 | 23.33 | 22.33 | 22.67 | 26.67 | 24.67 | 22.00 | 24.43 | 4 | 24.00 | 24.75 |
| SD | 3.27 | 3.39 | 3.50 | 3.78 | 3.93 | 3.62 | 2.76 | 4.31 | 4.21 | 4.27 |
| 11 | Mean | 21.83 | 23.33 | 23.33 | 21.83 | 26.50 | 21.50 | 22.33 | 23.64 | 6 | 23.88 | 23.88 |
| SD | 3.76 | 2.88 | 4.03 | 2.14 | 3.02 | 2.43 | 2.42 | 2.95 | 3.27 | 3.60 |
| **Glucose fasting, mmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 5.00 | 4.88 | 4.78 | 4.93 | 4.50 | 4.98 | 5.08 | 4.96 | –1 | 4.94 | 5.06 |
| SD | 0.39 | 0.50 | 0.29 | 0.23 | 0.23 | 0.31 | 0.18 | 0.30 | 0.29 | 0.37 |
| 2 | Mean | 5.07 | 5.32 | 4.92 | 4.92 | 4.87 | 5.03 | 5.00 | 5.01 | 2 | 5.19 | 5.11 |
| SD | 0.29 | 0.34 | 0.31 | 0.33 | 0.30 | 0.43 | 0.17 | 0.33 | 0.19 | 0.16 |
| 4 | Mean | 4.95 | 5.07 | 4.75 | 4.82 | 4.80 | 4.93 | 4.93 | 4.86 | 4 | 5.08 | 5.00 |
| SD | 0.26 | 0.32 | 0.27 | 0.17 | 0.35 | 0.24 | 0.15 | 0.31 | 0.16 | 0.21 |
| 11 | Mean | 4.92 | 4.95 | 4.92 | 4.67 | 4.70 | 4.93 | 4.98 | 4.84 | 6 | 5.04 | 4.96 |
| SD | 0.20 | 0.37 | 0.33 | 0.24 | 0.35 | 0.18 | 0.24 | 0.23 | 0.35 | 0.50 |
| **Inorganic phosphate, mmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 1.10 | 1.25 | 1.13 | 1.24 | 1.18 | 1.20 | 1.03 | 1.14 | –1 | 1.20 | 1.18 |
| SD | 0.14 | 0.12 | 0.14 | 0.09 | 0.16 | 0.06 | 0.06 | 0.13 | 0.23 | 0.13 |
| 2 | Mean | 1.13 | 1.22 | 1.12 | 1.22 | 1.17 | 1.24 | 1.19 | 1.23 | 2 | 1.17 | 1.22 |
| SD | 0.14 | 0.18 | 0.10 | 0.14 | 0.18 | 0.13 | 0.12 | 0.19 | 0.20 | 0.17 |
| 4 | Mean | 1.08 | 1.21 | 1.12 | 1.26 | 1.06 | 1.27 | 1.22 | 1.20 | 4 | 1.24 | 1.26 |
| SD | 0.14 | 0.21 | 0.17 | 0.14 | 0.17 | 0.11 | 0.11 | 0.21 | 0.18 | 0.22 |
| 11 | Mean | 1.08 | 1.27 | 1.09 | 1.27 | 1.04 | 1.12 | 1.14 | 1.10 | 6 | 1.15 | 1.23 |
| SD | 0.12 | 0.24 | 0.17 | 0.15 | 0.09 | 0.13 | 0.17 | 0.21 | 0.15 | 0.20 |
| **Lactate dfehydrogenase, IU/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 152.17 | 151.83 | 136.50 | 155.17 | 185.83 | 153.00 | 148.67 | 152.36 | –1 | 154.38 | 153.50 |
| SD | 9.62 | 17.96 | 15.72 | 21.06 | 28.14 | 11.30 | 20.29 | 17.52 | 19.70 | 23.50 |
| 2 | Mean | 147.67 | 139.83 | 129.83 | 146.67 | 163.17 | 145.00 | 131.33 | 137.93 | 2 | 129.63 | 128.00 |
| SD | 16.00 | 12.06 | 20.51 | 17.40 | 26.51 | 14.24 | 26.26 | 13.33 | 15.61 | 17.44 |
| 4 | Mean | 141.17 | 127.33 | 120.17 | 134.83 | 143.00 | 137.17 | 114.83 | 131.29 | 4 | 132.63 | 131.71 |
| SD | 9.24 | 9.97 | 14.76 | 20.91 | 22.15 | 5.27 | 22.68 | 10.56 | 14.65 | 20.57 |
| 11 | Mean | 152.33 | 148.00 | 133.17 | 167.67 | 161.67 | 146.67 | 136.17 | 151.43 | 6 | 161.75 | 158.13 |
| SD | 11.08 | 7.32 | 14.44 | 28.01 | 19.14 | 10.13 | 23.92 | 14.29 | 13.75 | 13.77 |
| **Potassium, mmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 4.75 | 4.92 | 4.55 | 4.67 | 4.67 | 4.98 | 4.82 | 4.82 | –1 | 4.50 | 4.76 |
| SD | 0.46 | 0.43 | 0.26 | 0.47 | 0.29 | 0.57 | 0.55 | 0.37 | 0.33 | 0.48 |
| 2 | Mean | 4.58 | 4.65 | 4.72 | 4.38 | 4.52 | 4.88 | 4.35 | 4.79 | 2 | 4.63 | 4.48 |
| SD | 0.21 | 0.41 | 0.28 | 0.15 | 0.33 | 0.21 | 0.40 | 0.46 | 0.54 | 0.18 |
| 4 | Mean | 4.78 | 4.82 | 4.60 | 4.88 | 4.47 | 5.10 | 4.72 | 4.88 | 4 | 4.55 | 4.50 |
| SD | 0.20 | 0.65 | 0.39 | 0.17 | 0.19 | 0.34 | 0.59 | 0.35 | 0.17 | 0.25 |
| 11 | Mean | 4.57 | 4.68 | 4.75 | 4.27 | 4.52 | 4.78 | 4.40 | 4.70 | 6 | 4.41 | 4.35 |
| SD | 0.24 | 0.37 | 0.49 | 0.37 | 0.31 | 0.62 | 0.24 | 0.33 | 0.34 | 0.36 |
| **Sodium, mmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 142.83 | 141.50 | 141.33 | 142.33 | 141.83 | 142.00 | 140.00 | 141.93 | –1 | 139.38 | 139.63 |
| SD | 1.33 | 2.07 | 1.03 | 2.07 | 1.47 | 2.28 | 1.67 | 1.49 | 1.60 | 2.45 |
| 2 | Mean | 141.17 | 141.50 | 142.33 | 142.00 | 139.17 | 142.33 | 139.67 | 141.43 | 2 | 138.88 | 139.38 |
| SD | 1.60 | 1.38 | 1.75 | 2.68 | 1.47 | 2.25 | 0.82 | 1.56 | 1.89 | 1.06 |
| 4 | Mean | 140.67 | 142.33 | 141.33 | 142.50 | 141.00 | 142.67 | 141.17 | 141.64 | 4 | 142.00 | 141.25 |
| SD | 1.97 | 2.16 | 1.03 | 1.38 | 1.41 | 2.16 | 0.98 | 1.91 | 1.41 | 1.04 |
| 11 | Mean | 142.17 | 142.00 | 142.00 | 141.00 | 142.17 | 141.17 | 140.17 | 142.07 | 6 | 141.50 | 141.50 |
| SD | 1.17 | 1.67 | 1.55 | 0.63 | 2.04 | 1.94 | 1.17 | 2.09 | 1.20 | 1.31 |
| **Total bilirubin, µmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 10.83 | 9.17 | 10.83 | 6.67 | 12.50 | 6.83 | 10.50 | 8.07 | –1 | 11.13 | 10.50 |
| SD | 4.83 | 2.79 | 3.37 | 1.51 | 4.59 | 1.17 | 3.02 | 3.08 | 6.08 | 6.89 |
| 2 | Mean | 14.33 | 13.00 | 14.33 | 12.83 | 11.67 | 14.17 | 13.50 | 11.86 | 2 | 13.63 | 13.25 |
| SD | 2.25 | 3.74 | 3.93 | 5.67 | 4.76 | 4.45 | 2.51 | 2.83 | 5.76 | 5.23 |
| 4 | Mean | 11.83 | 9.83 | 11.17 | 10.33 | 11.00 | 9.67 | 10.00 | 9.64 | 4 | 11.25 | 13.13 |
| SD | 1.60 | 2.32 | 2.79 | 4.37 | 2.28 | 2.34 | 2.00 | 3.13 | 5.15 | 5.06 |
| 11 | Mean | 13.00 | 6.17 | 9.33 | 7.50 | 8.33 | 10.00 | 7.50 | 8.00 | 6 | 9.50 | 11.75 |
| SD | 8.05 | 1.72 | 5.09 | 3.39 | 4.84 | 1.90 | 2.07 | 3.16 | 6.39 | 6.30 |
| **Total protein, g/L** |  | Protein |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 67.17 | 70.33 | 70.50 | 68.33 | 75.17 | 66.17 | 70.00 | 71.21 | –1 | 71.00 | 70.50 |
| SD | 4.36 | 4.46 | 5.79 | 5.79 | 4.36 | 3.76 | 2.00 | 4.95 | 4.47 | 4.99 |
| 2 | Mean | 68.33 | 73.00 | 71.67 | 73.33 | 72.17 | 74.17 | 70.83 | 71.79 | 2 | 69.25 | 69.63 |
| SD | 5.32 | 7.10 | 3.33 | 4.84 | 3.76 | 5.78 | 4.71 | 4.74 | 4.89 | 5.24 |
| 4 | Mean | 68.67 | 69.00 | 67.67 | 68.17 | 72.50 | 70.83 | 67.17 | 70.00 | 4 | 71.13 | 72.50 |
| SD | 4.84 | 7.01 | 2.88 | 4.02 | 5.47 | 4.17 | 5.12 | 5.82 | 4.64 | 6.87 |
| 11 | Mean | 68.17 | 68.00 | 69.83 | 68.00 | 72.00 | 66.33 | 68.67 | 69.93 | 6 | 70.63 | 71.25 |
| SD | 4.67 | 4.47 | 4.36 | 3.46 | 4.90 | 3.33 | 4.41 | 3.63 | 5.18 | 4.06 |
| **Urea, mmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 5.47 | 5.10 | 4.60 | 5.45 | 5.13 | 5.08 | 5.22 | 5.28 | –1 | 5.19 | 5.31 |
| SD | 1.19 | 0.74 | 0.94 | 2.43 | 1.36 | 0.95 | 1.16 | 1.02 | 1.25 | 1.19 |
| 2 | Mean | 4.35 | 4.72 | 4.28 | 4.67 | 4.32 | 5.23 | 5.07 | 4.64 | 2 | 4.30 | 4.65 |
| SD | 0.82 | 0.50 | 1.03 | 1.32 | 0.69 | 0.72 | 0.62 | 0.76 | 0.84 | 0.77 |
| 4 | Mean | 4.18 | 4.30 | 4.35 | 4.68 | 4.42 | 5.00 | 5.33 | 4.26 | 4 | 4.68 | 5.01 |
| SD | 1.03 | 0.37 | 1.01 | 1.21 | 0.78 | 0.57 | 0.82 | 0.79 | 0.85 | 0.58 |
| 11 | Mean | 5.08 | 4.30 | 4.30 | 5.12 | 4.10 | 4.97 | 5.60 | 4.78 | 6 | 4.58 | 4.66 |
| SD | 1.42 | 1.07 | 0.95 | 1.59 | 0.85 | 1.20 | 1.02 | 1.26 | 1.15 | 1.16 |
| **Uric acid, µmol/L** |  |  |  |  |  |  |  |  |  |  |  |  |
| –1 | Mean | 334.33 | 328.17 | 309.00 | 310.83 | 347.33 | 309.33 | 320.67 | 317.71 | –1 | 327.38 | 335.88 |
| SD | 52.07 | 52.38 | 27.72 | 47.00 | 20.96 | 34.05 | 39.41 | 46.04 | 77.35 | 27.35 |
| 2 | Mean | 330.33 | 343.50 | 316.50 | 310.17 | 352.33 | 335.00 | 333.33 | 328.64 | 2 | 333.75 | 297.88 |
| SD | 61.24 | 53.34 | 16.98 | 44.42 | 44.21 | 49.09 | 34.01 | 42.56 | 59.29 | 31.33 |
| 4 | Mean | 303.83 | 326.17 | 285.17 | 297.67 | 328.83 | 302.17 | 315.50 | 299.64 | 4 | 337.75 | 331.50 |
| SD | 53.39 | 46.40 | 15.82 | 42.79 | 52.82 | 39.95 | 34.38 | 35.28 | 33.24 | 37.30 |
| 11 | Mean | 333.00 | 326.50 | 307.17 | 290.33 | 315.33 | 308.33 | 338.50 | 322.64 | 6 | 318.50 | 331.75 |
| SD | 54.37 | 34.57 | 42.21 | 58.05 | 38.97 | 27.62 | 38.02 | 45.37 | 47.52 | 38.50 |

Table S5: Coagulation measures at baseline and change from baseline following single-dose P128 or placebo

| **Measure/****Study day** | **Part A** | **Part B** |
| --- | --- | --- |
| **Value** | **10 mg (N=6)** | **30 mg (N=6)** | **100 mg (N=6)** | **250 mg (N=6)** | **500 mg (N=6)** | **750 mg (N=6)** | **1000 mg (N=6)** | **Placebo (N=14)** | **Study day** | **250 mg fasted (N=8)** | **250 mg fed****(N=8)** |
| **INR** |  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline (–1) | Mean | 0.99 | 0.99 | 0.96 | 1.00 | 1.06 | 1.04 | 1.04 | 1.02 | –1 | 1.02 | 1.03 |
| SD | 0.03 | 0.03 | 0.03 | 0.05 | 0.09 | 0.05 | 0.07 | 0.06 | 0.03 | 0.04 |
| 11  | Mean change | 0.003 | 0.000 | 0.043 | 0.033 |  –0.018 |  –0.013 |  –0.007 | 0.001 | 6 | 0.02 | 0.02 |
| SD | 0.041 | 0.026 | 0.038 | 0.048 | 0.056 | 0.042 | 0.026 | 0.029 | 0.04 | 0.05 |
| **PTPT, secs** |  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline (–1) | Mean  | 30.83 | 31.67 | 30.83 | 31.50 | 32.50 | 32.50 | 33.67 | 32.07 | –1 | 30.63 | 29.88 |
| SD | 2.14 | 1.97 | 3.19 | 0.84 | 2.26 | 5.99 | 3.08 | 3.58 | 2.56 | 2.53 |
| 11  | Mean change |  –0.67 | 0.00 | 3.17 |  –1.67 |  –0.50 |  –2.67 | 0.00 | 0.00 | 6 | –0.88 | 1.5 |
| SD | 1.37 | 1.55 | 3.25 | 4.08 | 1.05 | 2.73 | 1.79 | 2.63 | 2.80 | 2.07 |
| **PTT** |  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline (–1) | Mean  | 11.00 | 11.00 | 10.50 | 11.0 | 11.50 | 11.33 | 11.17 | 11.14 | –1 | 11.00 | 11.13 |
| SD | 0.00 | 0.00 | 0.55 | 0.63 | 1.05 | 0.52 | 0.75 | 0.54 | 0 | 0.35 |
| 11  | Mean change |  –0.17 | 0.00 | 0.50 | 0.17 | 0.17 | 0.00 |  –0.17 | 0.07 | 6 | 0.25 | 0.13 |
| SD | 0.41 | 0.00 | 0.55 | 0.75 | 0.75 | 0.63 | 0.41 | 0.48 | 0.46 | 0.64 |

INR, international normalised ratio; PTPT, partial thromboplastin time; PTT, prothrombin time

Table S6: Baseline serum folate levels (µg/mL) and change in serum folate levels from baseline following single-dose P218 or placebo

| **Study day** | **Part A** | **Part B** |
| --- | --- | --- |
| **Value** | **10 mg (N=6)** | **30 mg (N=6)** | **100 mg (N=6)** | **250 mg (N=6)** | **500 mg (N=6)** | **750 mg (N=6)** | **1000 mg (N=6)** | **Placebo (N=14)** | **Study day** | **250 mg fasted (N=8)** | **250 mg fed****(N=8)** |
| Baseline (–1) | Mean | 6.42 | 7.02 | 9.40 | 7.35 | 9.72 | 6.53 | 7.25 | 8.28 | –1 | 6.51  | 5.44  |
| SD | 1.77 | 2.56 | 2.65 | 2.49 | 3.52 | 1.38 | 3.00 | 3.18 | 4.56  | 2.41  |
| 2  | Mean change | 0.63 | 0.23 | –0.33 | –0.55 | –1.83 | –0.97 | –0.27 | –0.49 | 2 | –1.27 | –0.93 |
| SD | 0.82 | 1.50 | 1.13 | 1.07 | 3.61 | 1.24 | 2.93 | 2.27 | 2.00 | 0.41 |
| 4  | Mean change | 0.68 | 0.47 | –0.5 | 0.62 | –0.87 | 0.43 | –0.02 | –0.09 | 4 | –0.61 | 0.14 |
| SD | 0.63 | 1.50 | 1.42 | 0.90 | 2.43 | 1.40 | 2.71 | 2.25 | 2.18 | 0.88 |
| 11 | Mean change | 0.42 | –0.05 | –0.63 | –1.00 | –0.78 | 1.10 | –0.18 | –0.74 | 6 | –1.41 | –0.24 |
| SD | 0.94 | 1.76 | 1.66 | 2.67 | 1.78 | 2.45 | 3.09 | 2.10 | 2.46 | 0.64 |

Figure S1: Geometric mean (±SD) plasma concentration–time profiles for P218 and metabolites following single P218 doses of 10–1000 mg



Table S7: Dose proportionality analysis of P218 single doses for P218 and metabolites

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Analyte** | **Measure** | **Geometric mean at P218 dose:** | **Slope** | **Confidence interval** | **Lack of fit test** |
| **10 mg****(N=6)** | **30 mg****(N=6)** | **100 mg****(N=6)** | **250 mg****(N=6)** | **500 mg****(N=6)** | **750 mg****(N=6)** | **1000 mg****(N=6)** | **90%** | **95%** | **DF** | **F value** | **P value** |
| P218 | Cmax (ng/mL) | 64.33 | 203.19 | 929.13 | 2093.29 | 4158.80 | 5979.78 | 8641.96 | 1.06 | 1.00, 1.11 | 0.99, 1.13 | 35 | 0.04 | 0.96 |
| AUClast (h.ng/mL) | 125.97 | 435.84 | 1574.05 | 3904.39 | 7731.40 | 13403.09 | 17608.63 | 1.06 | 1.02, 1.10 | 1.02, 1.11 | 35 | 0.03 | 0.97 |
| AUCinf (h.ng/mL) | 129.20 | 413.35 | 1578.35 | 3924.78 | 7757.98 | 13568.48 | 17814.77 | 1.07 | 1.03, 1.11 | 1.02, 1.12 | 32 | 0.19 | 0.97 |
| P218 β-acyl glucuronide | Cmax (ng/mL) | 140.42 | 384.45 | 1372.49 | 3807.83 | 4853.60 | 8325.86 | 12567.43 | 0.96 | 0.90, 1.02 | 0.89, 1.03 | 35 | 0.20 | 0.82 |
| AUClast (h.ng/mL) | 313.80 | 858.69 | 2857.73 | 8226.07 | 11459.20 | 22895.45 | 31835.68 | 0.99 | 0.94, 1.04 | 0.93, 1.05 | 35 | 0.03 | 0.97 |
| AUCinf (h.ng/mL) | 316.57 | 863.40 | 3111.35 | 8251.06 | 11494.98 | 22996.04 | 32077.15 | 0.99 | 0.94, 1.04 | 0.93, 1.05 | 34 | 1.09 | 0.38 |
| P218-OH | Cmax (ng/mL) | 3.16 | 9.81 | 35.98 | 57.74 | 110.94 | 143.65 | 192.70 | 0.87 | 0.82, 0.92 | 0.81, 0.93 | 35 | 0.03 | 0.97 |
| AUClast (h.ng/mL) | 11.89 | 46.87 | 160.62 | 312.94 | 619.88 | 863.77 | 1168.07 | 0.97 | 0.92, 1.01 | 0.91, 1.02 | 35 | 0.00 | 1.00 |
| AUCinf (h.ng/mL) | 13.37 | 49.48 | 163.76 | 322.63 | 650.81 | 890.45 | 1187.56 | 0.95 | 0.91, 1.00 | 0.90, 1.01 | 32 | 1.02 | 0.42 |
| P218-OH β-acyl glucuronide | Cmax (ng/mL) | 86.89 | 270.40 | 888.30 | 2288.02 | 2888.72 | 4539.26 | 6569.84 | 0.91 | 0.86, 0.96 | 0.85, 0.97 | 35 | 0.18 | 0.84 |
| AUClast (h.ng/mL) | 258.37 | 887.21 | 2479.41 | 6963.97 | 9672.66 | 17427.14 | 23715.16 | 0.95 | 0.91, 0.97 | 0.91, 1.00 | 35 | 0.02 | 0.98 |
| AUCinf (h.ng/mL) | 260.63 | 853.04 | 2595.61 | 6984.84 | 9719.67 | 16489.84 | 22295.25 | 0.95 | 0.91, 0.98 | 0.90, 0.99 | 30 | 1.77 | 0.15 |

Cmax, AUClast and AUCinf are described as geometric mean. AUClast, area under the concentration–time curve for the sampling period; AUCinf, area under the concentration–time curve extrapolated to infinity; Cmax, maximum plasma concentration; DF, degrees of freedom

Figure S2: Concentration–time profiles for P218 and metabolites in subjects administered P218 250 mg in the fasted or fed state.



Table S8: Categorical QTcF interval data following a single dose of P218 or placebo

|  |  |  |  |
| --- | --- | --- | --- |
| **Time** | **Category** | **Part A, n (%)** | **Part B, n (%)** |
| **10 mg (N=6)** | **30 mg (N=6)** | **100 mg (N=6)** | **250 mg (N=6)** | **500 mg (N=6)** | **750 mg (N=6)** | **1000 mg (N=6)** | **Placebo (N=14)** | **250 mg****Fasted****(N=8)** | **250 mg****Fed****(N=8)** |
| Day 1\* (0.5–8h) | <450 ms | 6 (100) | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| ≥450,<480 msec | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 |
| Day 2 (24h) | <450 ms | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Day 3 (48 h) | <450 ms | 6 (100) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Missing | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Day 4 (72 h) | <450 ms | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Day 6 (120 h) | <450 ms | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Day 8 (168 h) | <450 ms | 6 (100) | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 13 (92.9) | NA | NA |
| Missing | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (7.1) | NA | NA |
| Day 9 (192 h) | <450 ms | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 14 (100) | NA | NA |
| Missing | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | NA | NA |
| Day 11 | <450 ms | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | NA | NA |
| Missing | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | NA | NA |

\*ECGs were taken at 0.5, 1, 2, 4, 6, 7, 8 and 12 h post-dose; the value of ≥450,<480 msec occurred at 4 h post-dose; there was one missing value for the 30 mg dose at 1 h post-dose. For all other categories ('≥480 msec, <500 msec' and '≥500 msec') there were no observations

NA, ECG not taken as beyond study bounds

Table S9: Categorical QTcF interval data versus baseline following a single dose of P218 or placebo

|  |  |  |  |
| --- | --- | --- | --- |
| **Time** | **Category** | **Part A, n (%)** | **Part B, n (%)** |
| **10 mg (N=6)** | **30 mg (N=6)** | **100 mg (N=6)** | **250 mg (N=6)** | **500 mg (N=6)** | **750 mg (N=6)** | **1000 mg (N=6)** | **Placebo (N=14)** | **250 mg****Fasted****(N=8)** | **250 mg****Fed****(N=8)** |
| Day 1\* (0.5–8h) | Increase <30 msec | 6 (100) | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Day 2 (24h) | Increase <30 msec | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Day 3 (48 h) | Increase <30 msec | 6 (100) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Missing | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Day 4 (72 h) | Increase <30 msec | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Day 6 (120 h) | Increase <30 msec | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | 8 (100) | 8 (100) |
| Day 8 (168 h) | Increase <30 msec | 6 (100) | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 13 (92.9) | NA | NA |
| Missing | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (7.1) | NA | NA |
| Day 9 (192 h) | Increase <30 msec | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 14 (100) | NA | NA |
| Missing | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | NA | NA |
| Day 11 | Increase <30 msec | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 14 (100) | NA | NA |
| Missing | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | NA | NA |

\*ECGs were taken at 0.5, 1, 2, 4, 6, 7, 8 and 12 h post-dose; there was one missing value for the 30 mg dose at 1 h post-dose. For all other categories ('increase ≥30 msec, and increase ≥60 msec) there were no observations

NA, ECG not taken as beyond study bounds

Figure S3: Change in QTcF interval from baseline following a single dose of P218 or placebo



Table S10: Concentration–time data determined by LC-MS/MS analysis (limit of quantification 0.200 ng/mL) versus concentration–time data calculated from the *P. falciparum* antimalarial activity of P218 in serum samples

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Subject (dose)** | **Time (h)** | **Concentration LC-MS/MS (ng/ml)** | **Dilution factor** | **Highest concentration (ng/mL)** | **IC50 (ng/mL)** | **Reference IC50 /IC50 (ng/mL)** | **Calculated concentration (ng/mL)** | **Ratio of LC-MS/MS to calculated concentration** |
| 1 (250 mg) | 0 | <0.200 | – | – | – | – | – | – |
| 0.25 | <0.200 | – | – | – | – | – | – |
| 1 | 105.0 | 10 | 10.50 | 0.22 | 1.95 | 205.23 | 2.0 |
| 2 | 1850.0 | 200 | 9.25 | 0.19 | 2.26 | 4186.84 | 2.3 |
| 6 | 46.4 | 4 | 11.60 | 0.10 | 4.30 | 199.52 | 4.3 |
| 12 | 6.51 | 4 | 1.63 | 0.09 | 4.78 | 31.10 | 4.8 |
| 24 | 1.88 | 4 | 0.47 | 0.08 | 5.38 | 10.11 | 5.4 |
| 48 | 0.431 | 4 | 0.11 | 0.06 | 7.17 | 3.09 | 7.2 |
| 120 | <0.200 | – | – | – | – | – | – |
| 2 (250 mg) | 0 | <0.200 | – | – | – | – | – | – |
| 0.25 | <0.200 | – | – | – | – | – | – |
| 1 | 1240 | 1000 | 1.24 | 0.20 | 2.05 | 2542.00 | 2.1 |
| 2 | 2290 | 1000 | 2.29 | 0.12 | 3.42 | 7824.17 | 3.4 |
| 6 | 67.3 | 100 | 0.67 | 0.10 | 4.10 | 275.93 | 4.1 |
| 12 | 8.26 | 10 | 0.83 | 0.08 | 5.13 | 42.33 | 5.1 |
| 24 | 2.34 | 4 | 0.59 | 0.09 | 4.56 | 10.66 | 4.6 |
| 48 | 0.225 | 4 | 0.06 | 0.04 | 10.25 | 2.31 | 10.3 |
| 120 | <0.200 | – | – | – | – | – | – |
| 3 (250 mg) | 0 | <0.200 | – | – | – | – | – | – |
| 0.25 | 1.42 | – | – | – | – | – | – |
| 1 | 1670 | 1000 | 1.67 | 0.14 | 2.93 | 4890.71 | 2.9 |
| 2 | 481 | 500 | 0.96 | 0.14 | 2.93 | 1408.64 | 2.9 |
| 6 | 140 | 100 | 1.40 | 0.12 | 3.42 | 478.33 | 3.4 |
| 12 | 12.9 | 10 | 1.29 | 0.11 | 3.73 | 48.08 | 3.7 |
| 24 | 4.08 | 4 | 1.02 | 0.10 | 4.10 | 16.73 | 4.1 |
| 48 | <0.200 | – | – | – | – | – | – |
| 120 | <0.200 | – | – | – | – | – | – |
| 4 (250 mg) | 0 | <0.200 | – | – | – | – | – | – |
| 0.25 | <0.200 | – | – | – | – | – | – |
| 1 | 2410 | 1000 | 2.41 | 0.19 | 2.16 | 5200.53 | 2.2 |
| 2 | 1670 | 1000 | 1.67 | 0.17 | 2.41 | 4027.65 | 2.4 |
| 6 | 142 | 100 | 1.42 | 0.12 | 3.42 | 485.17 | 3.4 |
| 12 | 21.2 | 50 | 0.42 | 0.09 | 4.56 | 96.58 | 4.6 |
| 24 | 5.34 | 4 | 1.34 | 0.08 | 5.13 | 27.37 | 5.1 |
| 48 | 1.72 | 4 | 0.43 | 0.10 | 4.10 | 7.05 | 4.1 |
| 120 | <0.200 | – | – | – | – | – | – |
| 5 (250 mg) | 0 | <0.200 | – | – | – | – | – | – |
| 0.25 | 39.0 | 4 | 9.75 | 0.23 | 1.78 | 69.52 | 1.8 |
| 1 | 2500 | 1000 | 2.50 | 0.16 | 2.56 | 6406.25 | 2.6 |
| 2 | 1230 | 1000 | 1.23 | 0.14 | 2.93 | 3602.14 | 2.9 |
| 6 | 104 | 100 | 1.04 | 0.12 | 3.42 | 355.33 | 3.4 |
| 12 | 8.15 | 10 | 0.82 | 0.08 | 5.13 | 41.77 | 5.1 |
| 24 | 2.09 | 4 | 0.52 | 0.07 | 5.86 | 12.24 | 5.9 |
| 48 | 0.854 | 4 | 0.21 | 0.07 | 5.89 | 5.00 | 5.9 |
| 120 | 0.602 | 4 | 0.15 | – | – | – | – |
| 6 (250 mg) | 0 | <0.200 | – | – | – | – | – | – |
| 0.25 | 1.34 | 4 | 0.34 | – | – | – | – |
| 1 | 1570 | 1000 | 1.57 | 0.14 | 2.93 | 4597.86 | 2.9 |
| 2 | 465 | 500 | 0.93 | 0.13 | 3.15 | 1466.54 | 3.2 |
| 6 | 68.8 | 100 | 0.69 | 0.13 | 3.15 | 216.98 | 3.2 |
| 12 | 8.20 | 10 | 0.82 | 0.10 | 4.10 | 33.62 | 4.1 |
| 24 | 5.31 | 4 | 1.33 | 0.13 | 3.15 | 16.75 | 3.2 |
| 48 | 1.53 | 4 | 0.38 | 0.15 | 2.73 | 4.18 | 2.7 |
| 120 | 1.34 | 4 | 0.34 | – | – | – | – |
| 7 (500 mg) | 0 | <0.200 | 4 | – | – | – | – | – |
| 0.25 | 173.00 | 200 | 0.87 | 0.19 | 2.32 | 400.63 | 2.3 |
| 1 | 2420.00 | 2000 | 1.21 | 0.16 | 2.75 | 6655.00 | 2.8 |
| 2 | 8920.00 | 10000 | 0.89 | 0.19 | 2.32 | 20656.84 | 2.3 |
| 6 | 208.00 | 200 | 1.04 | 0.12 | 3.67 | 762.67 | 3.7 |
| 12 | 15.80 | 10 | 1.58 | 0.07 | 6.29 | 99.31 | 6.3 |
| 24 | 4.46 | 10 | 0.45 | 0.07 | 6.29 | 28.03 | 6.3 |
| 48 | 1.65 | 4 | 0.41 | 0.06 | 7.33 | 12.10 | 7.3 |
| 120 | <0.200 | 4 | – | – | – | – | – |
| 240 | <0.200 | 4 | – | – | – | – | – |
| 8 (500 mg) | 0 | <0.200 | 4 | – | – | – | – | – |
| 0.25 | 386.00 | 200 | 1.93 | 0.26 | 1.69 | 653.23 | 1.7 |
| 1 | 3430.00 | 2000 | 1.72 | 0.13 | 3.38 | 11609.23 | 3.4 |
| 2 | 1720.00 | 10000 | 0.17 | 0.16 | 2.75 | 4730.00 | 2.8 |
| 6 | 187.00 | 200 | 0.94 | 0.15 | 2.93 | 548.53 | 2.9 |
| 12 | 24.40 | 10 | 2.44 | 0.11 | 4.00 | 97.60 | 4.0 |
| 24 | 9.36 | 10 | 0.94 | 0.12 | 3.67 | 34.32 | 3.7 |
| 48 | 2.66 | 4 | 0.67 | 0.12 | 3.67 | 9.75 | 3.7 |
| 120 | <0.200 | 4 | – | – | – | – | – |
| 240 | <0.200 | 4 | – | – | – | – | – |
| 9 (500 mg) | 0 | <0.200 | 4 | – | – | – | – | – |
| 0.25 | <0.200 | 4 | – | – | – | – | – |
| 1 | 1410.00 | 2000 | 0.71 | 0.16 | 2.75 | 3877.50 | 2.8 |
| 2 | 5740.00 | 10000 | 0.57 | 0.17 | 2.59 | 14856.47 | 2.6 |
| 6 | 172.00 | 200 | 0.86 | 0.09 | 4.89 | 840.89 | 4.9 |
| 12 | 22.60 | 10 | 2.26 | 0.08 | 5.50 | 124.30 | 5.5 |
| 24 | 8.78 | 10 | 0.88 | 0.09 | 4.89 | 42.92 | 4.9 |
| 48 | 3.20 | 4 | 0.80 | 0.08 | 5.50 | 17.60 | 5.5 |
| 120 | <0.200 | 4 | – | – | – | – | – |
| 240 | <0.200 | 4 | – | – | – | – | – |
| 10 (500 mg) | 0 | <0.200 | 4 | – | – | – | – | – |
| 0.25 | <0.200 | 4 | – | – | – | – | – |
| 1 | 3640.00 | 2000 | 1.82 | 0.18 | 2.44 | 8897.78 | 2.4 |
| 2 | 2690.00 | 2000 | 1.35 | 0.18 | 2.44 | 6575.56 | 2.4 |
| 6 | 118.00 | 200 | 0.59 | 0.12 | 3.67 | 432.67 | 3.7 |
| 12 | 8.98 | 10 | 0.90 | 0.08 | 5.50 | 49.39 | 5.5 |
| 24 | 2.85 | 4 | 0.71 | 0.06 | 7.33 | 20.90 | 7.3 |
| 48 | 0.36 | 4 | 0.09 | 0.03 | 14.67 | 5.32 | 14.8 |
| 120 | <0.200 | 4 | – | – | – | – | – |
| 240 | <0.200 | 4 | – | – | – | – | – |
| 11 (500 mg) | 0 | <0.200 | 4 | – | – | – | – | – |
| 0.25 | 0.39 | 4 | 0.10 | – | – | – | – |
| 1 | 112.00 | 200 | 0.56 | 0.20 | 2.20 | 246.40 | 2.2 |
| 2 | 2960.00 | 2000 | 1.48 | 0.19 | 2.32 | 6854.74 | 2.3 |
| 6 | 329.00 | 200 | 1.65 | 0.16 | 2.75 | 904.75 | 2.8 |
| 12 | 24.10 | 200 | 0.12 | 0.11 | 4.00 | 96.40 | 4.0 |
| 24 | 5.89 | 10 | 0.59 | 0.12 | 3.67 | 21.60 | 3.7 |
| 48 | 2.95 | 4 | 0.74 | 0.12 | 3.67 | 10.82 | 3.7 |
| 120 | <0.200 | 4 | – | – | – | – | – |
| 240 | <0.200 | 4 | – | – | – | – | – |
| 12 (500 mg) | 0 | <0.200 | – | – | – | – | – | – |
| 0.25 | <0.200 | – | – | – | – | – | – |
| 1 | 4820.00 | 2000 | 2.41 | 0.14 | 3.14 | 15148.57 | 3.1 |
| 2 | 1800.00 | 2000 | 0.90 | 0.16 | 2.75 | 4950.00 | 2.8 |
| 6 | 89.70 | 200 | 0.45 | 0.09 | 4.89 | 438.53 | 4.9 |
| 12 | 17.20 | 10 | 1.72 | 0.08 | 5.50 | 94.60 | 5.5 |
| 24 | 3.41 | 4 | 0.85 | 0.05 | 8.80 | 30.01 | 8.8 |
| 48 | 1.08 | 4 | 0.27 | 0.06 | 7.33 | 7.92 | 7.3 |
| 120 | <0.200 | 4 | – | – | – | – | – |
| 240 | <0.200 | 4 | – | – | – | – | – |

Figure S4. Comparison of concentration–time profiles determined by LC-MS/MS analysis (limit of quantification 0.200 ng/mL) versus concentration–time data calculated from the *P. falciparum* antimalarial activity of P218 in serum samples following a 250 mg or 500 mg single dose of P218

