Evaluation of the Equivalence of Different Intakes of Fruitflow® in Affecting Platelet Aggregation and Thrombin Generation Capacity in a Randomized, Pilot Study in Male Subjects

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Research Article

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Abstract

Background

We aimed to investigate the range of intakes linked to efficacy and to make an initial assessment of variability in response to the water-soluble tomato extract, Fruitflow®. Platelet response to ADP agonist and thrombin generation capacity were monitored at baseline and 24h after consuming 0,30,75,150,300mg of Fruitflow® in a randomized, double-blinded crossover study in male subjects 30–65 years of age (n=12, ISRCTN53447583,24/02/2021).

Results

Results showed that the changes from baseline aggregation (-12.0±13.9 to -17.7±15.7%) and thrombin generation (-8.6±4.1 to -11.3±2.3%) achieved for the 75mg, 150mg, and 300mg supplements were equivalent. Effects observed for 0 mg and 30mg supplements were non-equivalent to 150mg and not different from baseline (aggregation changed by -0.7±10.2 to 3.0±5.0%, thrombin generation by 0.8±3.1%).

Conclusions

The data suggest that the efficacious range for Fruitflow® lies between 75mg and 300mg, depending on the individual. It may be pertinent to personalize the daily intake of Fruitflow® depending on individual platelet response.

Introduction

Dietary antiplatelets become of greater interest as the range of application for such interventions becomes more evident in primary prevention. We have previously researched the response of platelets to the natural antiplatelet Fruitflow® (1, 2) a water-soluble tomato extract containing a range of antiplatelet compounds and marketed globally as a naturally-derived supplement, with a health claim approved by the European Commission when taken daily at a dosage of 150mg (3, 4). From previous studies, a dose of 150mg Fruitflow® generally causes approximately 15 – 23% suppression of platelet response to 3 mmol/L ADP agonist. This is a platelet suppression that is not associated with increased bleeding tendencies and thus safe for use by the general population (1).

We know from previous work that as much as a threefold increase in Fruitflow® dosage does not result in a significantly higher effect on platelet aggregation (5), but no data exists on doses lower than 150mg Fruitflow® per day. Thus, the lower limit of the efficacious dose range is not yet known. In studies in healthy individuals, we have also observed marked variability in the Fruitflow® response range (1-3). The degree of variability makes it likely that some individuals will be more responsive to Fruitflow than others, and thus may achieve the desired platelet inhibition at lower doses.
Here we describe a pilot study (Clinical trial Registration Number ISRCTN53447583, Date of Registration 24/02/2021) that set out to test different doses of Fruitflow® in a small number of subjects to establish whether doses other than the current standard dose of 150mg would affect platelet function in a similar manner and to examine the heterogeneity of the response.

Materials & Methods

Fruitflow® SD is commercially produced by DSM Nutritional Products, Basel, Switzerland, in powder format. The composition of Fruitflow® has been described previously(1). Briefly, a standard 150mg dose (as per the approved EC health claim) delivers up to 9 mg nucleoside derivatives, up to 10 mg simple phenolic conjugates (e.g., chlorogenic acid, other caffeic/phenolic acid derivatives), and up to 7 mg flavonoid derivatives, of which at least 2.4mg are quercetin derivatives. The commercially produced Fruitflow® SD is standardized to ensure minimum quantities of these three compound groups are contained in each manufactured ingredient batch, ensuring that the bioactive components’ intake is consistent from batch to batch. In this study, the powder was administered as a single dose at concentrations of 30mg, 75mg, 150mg, and 300mg Fruitflow® SD (FF30, FF75, FF150, FF300). Tapioca starch was used as a placebo control (Con) (Essential Nutrition Ltd, Brough, UK). All supplements were encapsulated using size 00 Vegecaps (LGA, La Seyne-sur-Mer, France), and the final weight of each capsule was 600g (weight of Fruitflow® SD plus weight of tapioca starch filler). Capsules were coded following a randomization protocol: Genstat (VSN International, 17th /18th edition) was used to generate 20 sets of randomly allocated treatments numbered 1-5. Each treatment set was allocated to a subject number, in numerical order, and the appropriate treatments were boxed and labelled with the subject number and visit number, e.g., S1-1, S1-2, S1-3, etc. All supplements were coded off-site at the Human Nutrition Unit of the University of Aberdeen and provided to the investigators prior to the start of recruitment. Subject numbers were then assigned to subjects in order of recruitment into the study. Supplements were identical concerning appearance and only differed in the coding of the capsules. The treatment code of the intervention supplements was blinded for subjects, investigators, and staff involved in the study’s conduct.

Subjects

15 adult males aged 30–65 years were assessed for eligibility, of which 12 were recruited into the study. Recruitment was carried out by the local population, by poster advertisement within the Faculty of Medicine. Study numbers were estimated on the basis of the expected response to the 150mg dosage: 15 – 20% ± 9 - 15% reduction from baseline ADP-mediated aggregation after 150mg Fruitflow® SD. For such a response, we calculated a minimum of 10 subjects required to allow the effect to be detected (vs. placebo) with 80% power and a 95% confidence interval for the mean. Extra subjects were recruited to allow for failure to complete all interventions. Suitability for inclusion into the study was assessed using diet and lifestyle questionnaires and medical screening, during which blood pressure and platelet function were evaluated. Individuals with low haematology counts (platelet number < 170 x 10⁹/ L;
haematocrit < 40% for males or < 30% for females; haemoglobin < 120 g/L for males or <110 g/L for females), or low platelet function (as determined by response to 3 mmol/L ADP agonist) were not included into the study. Any subject habitually consuming dietary supplements (for example, fish oils, evening primrose oil) suspended these supplements for a minimum of 1 month before participating in the study. Written informed consent was obtained from all subjects prior to participation, and all study procedures were in accordance with the Helsinki Declaration of 1975 (revised in 1983). The local ethical committee approved the study at Oslo University Hospital, Norway (Reference No.: 2015/ 396) and it was subsequently registered as ISRCTN53447583.

**Study design**

This was an active control equivalence study (a positive control study), following a double-blinded, randomized crossover design, in which the treatment interventions Con, FF30, FF75, and FF300 were compared to FF150 (standard dose). Subjects undertook all five interventions, with each intervention separated by a period of at least seven days. All study activities were undertaken at the Nutrition Dept. of the Faculty of Medicine, University of Oslo, Norway. Each intervention period was of 24-hour duration. Subjects presented at the Nutrition Department facility, and baseline measurements, including fasted baseline blood samples, were taken (t0). The intervention supplements, randomly assigned and blinded, were consumed in the presence of study investigators after the baseline venepuncture. Breakfast was then supplied, and subjects were free to leave the facility. After 24 hours, subjects returned to the facility, and a 12-hour fasted blood sample was taken for analysis (t24). Subjects were again given breakfast and were free to leave the facility, returning after a minimum of seven days to repeat the procedure for the next interventions, as required, until all five interventions had been completed.

**Study measurements**

*Platelet aggregation assay*

For measurement of platelet aggregation at baseline (t0) and post-intervention (t24), blood was mixed with 3·8% trisodium citrate (9:1 (v/v), blood/citrate). Blood collection using the Monovettes system (Sarstedt, UK), platelet-rich plasma (PRP) preparation, and light-transmission aggregometry were carried out as described by us previously (ref) (ref). Briefly, the platelet number in PRP was adjusted to 300 x 10⁹ / L with autologous platelet-poor plasma (PPP). Platelet aggregation in 200mL adjusted PRP was initiated by the addition of 20mL of ADP (Helena Laboratories, Beaumont, TX) at a range of concentrations that were pre-determined for each individual at the pre-intervention baseline. Based on the pre-intervention baseline measurements, an ADP concentration was selected for each individual, such that an optimal response could be recorded for each. Concentrations ranged from 1 – 8 mmol/L ADP. The aggregation progress was monitored in an AggRam 8-channel aggregometer (Helena Biosciences, Sunderland, UK) and quantified as area under the aggregation curve (%AUC). All measurements were carried out in duplicate, within 2 hours of blood sampling.
Effects on platelet aggregation observed post-intervention were expressed as the percentage change in %AUC post-intervention compared with baseline values.

**Thrombin generation capacity (TGC) assay**

Measurement of thrombin generation capacity is based on monitoring the fluorescence generated by thrombin cleavage of a fluorogenic substrate over time upon activation of the coagulation cascade by different concentrations of tissue factor and negatively charged phospholipids. The concentration of thrombin (nmol/L) in the sample can be calculated from the changes in fluorescence over time using a thrombin calibration curve.

Thrombin generation capacity (TGC) was measured at baseline (t0) and post-intervention (t24) in citrated platelet-poor plasma, which was further treated to ensure only microparticles remained in the plasma (no platelets or large platelet fragments). In this way, the TGC related to plasma microparticle load was measured. Aliquots of 25 mL were stored frozen at -80 °C for up to one month before analysis. Analyses were carried out using the Technothrombin® Thrombin Generation Assay (Diapharma Group Inc, West Chester, Ohio, US), using the protocol specified by the manufacturer but with some modification to sample preparation: platelet-poor plasma was generated by double centrifugation directly from citrated whole blood, not sequentially after generation of platelet-rich plasma. The final concentrations of tissue factor (TF) used were 1 pmol/L. Microparticle-free plasma and microparticle-high plasma (Diapharma Group Inc, West Chester, Ohio, US) were used as negative and positive controls.

**Supplementary measurements**

After each blood withdrawal, full blood counts were performed on EDTA anticoagulated blood using a hematology analyzer (Hemocytometer, Horiba ABX micros60, Montpellier, France) to monitor haematological parameters. Baseline plasma C-reactive protein (CRP) concentration was measured in EDTA-anticoagulated blood using a semi-quantitative latex agglutination assay (Dade Behring, Milton Keynes, UK), which allowed classification of sample CRP status as either ‘normal’ or ‘elevated’ (>6 ng/ml CRP). Data from samples with elevated CRP was discarded.

**Statistical analysis**

Data are presented as mean ± standard deviation (SD). Data from interventions where evidence of platelet pre-activation due to venepuncture existed or where elevated CRP was recorded were removed from the set. Preliminary assessment of the data distribution was carried out by inspecting histograms, and data points classified as outliers were removed. Changes from baseline (t0) within the study population were analysed using a mixed model following the residual maximum likelihood (REML) approach. Initially, random effect terms were subject / (visit x timepoint), while fixed effect terms were (order + treatment) x timepoint. Significance was tested with the Wald statistic. As no significant order x treatment interactions were observed, the model was simplified (without the order term, treatment and visit are equivalents). Random effects then became subject / (treatment x timepoint), and fixed effects
were treatment x timepoint. Treatments Con, FF30, FF75 and FF300 were compared to FF150, to determine equivalence or non-equivalence. Due to the small sample size, no post-hoc comparisons were made. Statistical analyses were carried out using Genstat (VSN International, 17th / 18th edition), and differences were considered significant at P < 0.05.

Results

Subject characteristics

In all, twelve subjects were recruited into the study, of which ten completed the intervention pattern (see Figure 1 for a participant flow diagram). The characteristics of the subject group (n=10) at the pre-intervention baseline are shown in Table 1. Subjects were of Asian ethnicity, with one smoker. Eight out of ten subjects were overweight or obese, and only one had a waist/hip ratio < 0.9. Nine out of ten subjects were characterised by hypertension – one with elevated BP (systolic BP 120-130, diastolic BP < 80 mm Hg), five with stage 1 hypertension (systolic BP 130 – 140 and/or systolic BP > 80 mm Hg) and two with stage 2 hypertension (BP > 140/90 mm Hg). Haemostatic variables were within the normal range and did not differ significantly from the pre-intervention baseline at any of the t0 timepoints. However, the average mean platelet volume (MPV) was relatively elevated, indicating some degree of platelet activation. A wide range of response to ADP agonist was observed, with concentrations ranging from 1 mmol/L to 8 mmol/L generating an optimal response in different individuals. The range observed for TGC was smaller, giving a more homogenous data set. The baseline levels of TGC measured were also relatively elevated, compared to a healthy population. These characteristics generally lead to the conclusion that some degree of platelet hyperaggregability could be expected in this set of subjects.

Intervention with different doses of Fruitflow® affected platelet function and TGC at t24

Table 2 shows the platelet aggregation response to optimal concentrations of ADP agonist in PRP at baseline (t0) and after the intervention (t24), and also sets out the percentage change from t0 after the intervention. Baseline measurements were not significantly different between visits. Treatment effects were observed at t24, with FF75, FF150, and FF300, all significantly reducing the platelet response to ADP, relative to t0, whereas no such effect was observed for Con or FF30. Data for TGC are also shown in Table 2; again, there was no difference between t0 measurements between treatments. TGC was affected similarly to platelet aggregation at t24; TGC was reduced by 15 – 20% relative to baseline for FF75, FF150, and FF300, but was not significantly reduced for Con or FF30.

Treatment with either FF75, FF150, or FF300 gave equivalent results

Treatment with FF75 or FF300 was equivalent to treatment with FF150, with all interventions reducing platelet response to ADP agonist by 12 – 18%. Treatments Con and FF30 were non-equivalent to FF150. A similar pattern was observed for TGC, with treatments FF75 and FF300 again showing equivalence to FF150, while treatments Con and FF30 did not.
Underlying heterogeneity in platelet response to ADP agonist leads to variable responses to Fruitflow® at all doses

The response to Fruitflow® at the different doses examined was variable, as reflected in the changes from baseline aggregation measured at optimal concentrations of ADP (Table 2, Figure 2).

TGC followed the same patterns of response to Fruitflow® as platelet aggregation but resulted in a more homogenous data set

Inspection of the TGC data shows a tighter range at the pre-intervention baseline (Table 1), and a smaller SD in the post-intervention responses to treatment (Table 2, Figure 2), compared to the platelet aggregation data at either concentration of ADP. Reductions in TGC for FF75, 150, and FF300 show a trend towards a dose-response, whereas the corresponding aggregation data are too variable for such a trend to be observed (Figure 2). The two treatments, which are non-equivalent to FF150 (Con and FF30), are also more similar to each other when considering TGC compared to when considering aggregation response, suggesting that there may be a specific reason behind the rise in platelet aggregation observed after intervention with FF30.

Discussion

Our aims in this pilot study were to examine whether consuming amounts of Fruitflow® less than 150mg could result in desirable levels of platelet suppression ex vivo, and to assess the platelet response variability to all doses tested. By doing so, we hoped to establish the lower limits of the efficacious intake level, and also to assess the potential value of personalizing the daily intake, based on individual response. The latter aim reflects a recent focus of study on the heterogeneity of platelet response to intervention – demographic and lifestyle-driven differences in platelet behaviour (6-9). Platelet behaviour varies in response to a wide range of factors – ethnicity, age, nutrition status, exposure to air pollution, exercise levels, etc. (10-19). No two individuals’ platelets are precisely the same, something that can be clearly observed in the heterogeneity of their responses to agonist and to antiplatelet agents(20-24), Studies using antiplatelet drugs have shown that marked differences in platelet responses may be linked to such factors, with genomic and nutrigenomic reasons postulated(25, 26). The approach to antiplatelet medication in secondary prevention has begun to evolve, as it becomes clearer that different demographics may respond very differently to fixed doses of antiplatelets(27-29). This is equally true for dietary antiplatelets, raising the prospect that personalization of the daily intake could be beneficial for optimal effects.

The study was small, and biased, in that all participants were male and from the Indian Subcontinent, and its size necessarily constrained the comparisons between Fruitflow® doses. It was intended to give an indication of the range of intakes displaying efficacy, rather than definitive data. The subjects displayed characteristics consistent with some degree of platelet hyperaggregability, which, although quite typical in the wider population, is a further slight bias.
The platelet aggregation response to ADP agonist was the main outcome measure, and TGC of platelet-depleted plasma was also included as a comparative measure. TGC is a standardized global haemostasis assay that is becoming well established: it incorporates both negative and positive controls(30, 31). It can be used to examine both thrombin generation kinetics and peak thrombin generation. Generation of thrombin is strongly linked to the concentration of circulating platelet microparticles and thus to platelet hyperaggregability. It is a more flexible method of analysis than platelet aggregometry and more suited to a quick assessment of individual haemostatic status. The ISTH published proposals to standardize sampling and analytical procedures for TGC in 2017(32), and Dargaud et al. subsequently suggested the use of TGC as a predictive tool to personalize the use of clotting factor replacement in haemophiliacs(33). TGC was included in this study as an outcome measure to examine whether TGC might be an effective measure of the effects of Fruitow®.

Our study found that, when compared to the current standard 150mg daily intake of Fruitow®, intakes of 75mg and 300mg gave equivalent results in terms of both platelet aggregation reduction and TGC reduction, with average ranges of response from 12 – 18 % for reduction of ADP-mediated aggregation, and from 15 – 20% for TGC. The control and the 30mg supplements were not equivalent to the 150mg dose, with neither causing a significant change from baseline aggregation. Thus, doses of Fruitow® from 75mg – 300mg affected platelet function equivalently in this group of subjects. The observation that 150mg and 300mg intakes are equivalent corresponds to findings from our earlier work which also showed that increasing intakes of Fruitow did not significantly increase the platelet suppression observed, compared to the ‘standard’ intake(2).

The baseline platelet response to ADP agonist was highly variable. Some subjects’ platelets showed 8 times more sensitivity of response to ADP than others, as judged from the agonist concentrations needed to give an optimal aggregation curve (range 1mmol/L – 8mmol/L ADP). Thus, it is no surprise that the range of responses to Fruitow® was similarly heterogeneous, although less so than in other studies. This may have been due to the subject characteristics – the subjects were quite similar in terms of ethnic background and some physical characteristics (e.g., BMI, presence of mild hypertension). Due to the small study size, we could not investigate whether platelets that respond more sensitively to ADP respond more, or less, sensitively to Fruitow® at this time.

Results obtained using TGC were less variable than those based on aggregometry. They showed a trend towards a dose-response, although the study design did not allow proper analysis of this. Using TGC as a surrogate biomarker for platelet hyperactivity or the platelet response to intervention is an interesting option, especially when the intervention period is less acute – similar to MPV, the full effect of any intervention on TGC is more likely to be observed over a longer timeframe. While TGC in platelet-depleted plasma cannot replace aggregometry in determining the purely platelet-specific response to an intervention, it does provide a linked estimate of microparticle-driven thrombin generation. Data already exists to give normal, low, and elevated TGC ranges in some patient populations, and the method is automatable and has increased flexibility compared to aggregometry.
Despite the limitations of this study, the data generated suggests that a larger study which addresses the bias contained in this pilot study should be undertaken to confirm that the efficacious dose range for Fruitflow® is between 75mg and 300mg; that personalizing the dosage of Fruitflow® could be an option to deliver optimal effects, given the observable heterogeneity of the response between individuals; and besides, that further investigation of TGC as a surrogate marker for monitoring the effects of the intervention on platelet function is warranted.

Declarations

Ethical approval and consent to participate

The local ethical committee Regionale Komiteer for Medisinsk og Helsefaglig Forskningsetikk (REK) sør-Øst approved the study at Oslo University Hospital, Norway (Reference No.: 2015/ 396), and it was subsequently registered as ISRCTN53447583. Written informed consent was obtained from all subjects prior to participation, and all study procedures were in accordance with the Helsinki Declaration of 1975 (revised in 1983).

Consent for publication

Consent for publication was included in the informed consent form signed by all subjects.

Availability of data and materials

Analysed data relevant to the study are included in the article. The datasets generated are not publicly available as set out in agreements with the commercial partners but are available from the corresponding author on reasonable request.

Competing interests

Ranjit K Das, Tanushree Dutta, and Dipankar Biswas declare no conflict of interest. Dr. Niamh O’Kennedy is the chief scientific officer of Provexis PLC. Dr. Ruedi Duss is employed by DSM Nutritional Products, Switzerland, and Professor Asim K. Duttaroy is a member of the Scientific Advisory Board of Provexis PLC.

Funding

Funding for this study was provided by DSM Nutritional Products Ltd, Kaiseraugst, Switzerland; supplements and supplementary analysis were provided by Provexis plc, UK.

Authors' contributions

The study was conceived and designed by AKDR, NOK and RD. Data collection and analysis was carried out by RKD, TD and DB. The manuscript was drafted by NOK, reviewed by AKDR and RD, and submitted by AKDR.
References


Tables

Table 1. Baseline characteristics of the subject group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-intervention baseline values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of origin</td>
<td>Indian Subcontinent</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 9 (40 - 65)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.6 ± 3.4 (22.2 - 34.0)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1 smoker, 9 non-smokers</td>
</tr>
<tr>
<td>Resting blood pressure (mm Hg)</td>
<td>134 ± 10 / 85 ± 9 (120/70 - 150/100)</td>
</tr>
<tr>
<td>Waist / hip ratio</td>
<td>1.00 ± 0.00 (0.89 - 1.04)</td>
</tr>
<tr>
<td>Mean platelet volume (MPV)</td>
<td>9.0 ± 0.8 (7.6 - 11.3)</td>
</tr>
<tr>
<td>Baseline platelet response to low ADP agonist (%AUC)</td>
<td>77.6 ± 15.1 (48.2 - 96.0)</td>
</tr>
<tr>
<td>Baseline platelet response to high ADP agonist (%AUC)</td>
<td>77.1 ± 10.0 (53.3 - 96.0)</td>
</tr>
<tr>
<td>Thrombin generation capacity</td>
<td>331 ± 54 (254 - 420)</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD, with the range given in brackets. n = 10. Low ADP agonist concentrations are defined as 1 – 3 mmol/L. High ADP agonist concentrations are defined as 5 – 8 mmol/L.

Table 2. Platelet aggregation response to ADP and thrombin generation capacity at t0 and t24, for each intervention undertaken by the subject group.
<table>
<thead>
<tr>
<th></th>
<th>Con</th>
<th>FF30</th>
<th>FF75</th>
<th>FF150</th>
<th>FF300</th>
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<tr>
<td><strong>Platelet aggregation in response to optimal ADP %AUC</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>t0</td>
<td>72.7 ± 17.6</td>
<td>71.0 ± 12.2</td>
<td>73.6 ± 12.8</td>
<td>74.5 ± 14.9</td>
<td>82.7 ± 13.1</td>
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<tr>
<td>t24</td>
<td>76.0 ± 15.7</td>
<td>75.7 ± 13.7</td>
<td>64.5 ± 16.3*</td>
<td>71.2 ± 17.6*</td>
<td>70.3 ± 20.4*</td>
</tr>
<tr>
<td>D% from t0</td>
<td>3.0 ± 5.0 §</td>
<td>-0.7 ± 10.2 §</td>
<td>-12.9 ± 17.7</td>
<td>-12.0 ± 13.9</td>
<td>-17.7 ± 15.7</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>TGC</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>t0</td>
<td>324 ± 53</td>
<td>327 ± 59</td>
<td>330 ± 57</td>
<td>333 ± 56</td>
<td>328 ± 59</td>
</tr>
<tr>
<td>t24</td>
<td>327 ± 53</td>
<td>330 ± 62</td>
<td>303 ± 58*</td>
<td>303 ± 53*</td>
<td>291 ± 54*</td>
</tr>
<tr>
<td>D% from t0</td>
<td>0.8 ± 3.0 §</td>
<td>0.8 ± 3.1 §</td>
<td>-8.6 ± 4.1</td>
<td>-9.2 ± 3.1</td>
<td>-11.3 ± 2.3</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. n = 10. ADP agonist concentrations ranged from 1 - 8 mmol/L. No significant differences between t0 values were detected between interventions. Where t24 is different from t0, this is indicated with *, while non-equivalence to FF150 is indicated by § (P < 0.05).

**Figures**
Figure 1

Study participant flow diagram Flow diagram showing the disposition of subjects throughout the screening, randomization and intervention stages of the study.
Figure 2

Platelet Aggregation Response Boxplots constructed to show the range of the $\Delta$% from baseline recorded for each treatment, for platelet aggregation (Max % AUC) at optimal ADP concentrations (Figure 2A), and TGC (Figure 2B). $n = 10$. ADP agonist concentrations ranged from 1 - 8 $\mu$mol/L. Median values are shown within the plots as the conventional line. Mean values (as given in Table 2) are shown for convenience, denoted by the marker x within each plot. Non-equivalence to FF150 is indicated by * ($P < 0.5$)