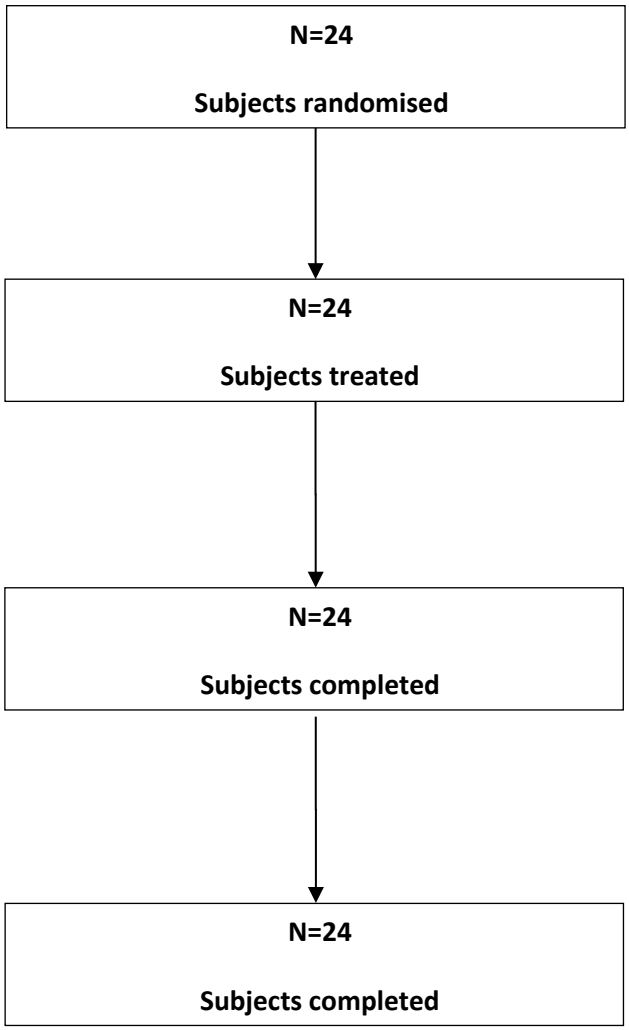
1. Participant Flow

Figure 1 Subject Disposition (Enrolled set):



2. Baseline Characteristics

Demographics and Baseline Characteristics (Enrolled, safety and PK sets) are presented below:

Characteristics	
Gender, n (%)	
Male	24 (100%)
Race, n (%)	
White	21 (87.5%)
Other	3 (12.5%)
Mulatto	2 (8.3%)
Mestizo	1 (4.2%)
Age, years (SD)	39.1 (6.9)
Height, cm (SD)	176.8 (5.9)
Body Weight, kg (SD)	79.60 (6.99)
BMI, kg/m^2 (SD)	25.50 (2.22)

After inclusion, all the 24 subjects took all the planned doses of the following Investigational Medicinal Products (IMPs) and completed the study:

- IMP1 (interacting drug): Netupitant/palonosetron 300mg/0.50 mg hard gelatine capsules (NEPA FDC) (Akynzeo®)
- IMP2 (substrate): Dexamethason 4 mg Jenapharm® (DEXA), dexamethasone 4 mg tablets

3. Outcome Measures

Primary Outcome Measure: Pharmacokinetics

After administration of a single capsule of NEPA FDC, the duration of CYP3A4 inhibition was investigated up to 10 days using dexamethasone as a probe substrate. The outcome of the statistical comparisons of the dexamethasone PK parameters measured on Days 1, 4, 6, 8 and 10 after the administration of DEXA alone with those after the administration of DEXA with NEPA FDC is summarized in following table:

Table 3 Statistical comparisons of the primary variable, AUC0-t of dexamethasone from Day 1 to Day 10, after administration of DEXA alone with that after administration of DEXA with NEPA FDC:DAY	**Treatment**	**AUC_{0-t} (h·ng/mL)**	**PE (%)**	**90% CI Lower limit (%)**	**90% CI Upper limit (%)**
Day 1	DEXA DEXA+NEPA	664.26 1052.53	158.45	150.98	166.29
Day 4	DEXA DEXA+NEPA	295.13 711.07	240.93	229.96	252.42
Day 6	DEXA DEXA+NEPA	376.08 561.81	149.39	143.05	156.00
Day 8	DEXA DEXA+NEPA	422.48 507.96	120.23	115.51	125.16
Day 10	DEXA DEXA+NEPA	448.71 498.66	111.13	107.23	115.17

DEXA: dexamethasone administered alone; DEXA+NEPA: dexamethasone administered with netupitant-palonosetron fixed-dose combination; PE (%): point estimate; CI (%): confidence intervals; geometric mean is shown for AUC_{0-t}

The statistical comparison of the primary variable AUC_{0-t} of dexamethasone after administration of DEXA alone and DEXA with NEPA FDC for all treatment days shows that cessation of the metabolic interaction between netupitant and dexamethasone occurred between Day 8 and Day 10. The upper limit of the 90% confidence interval of the point estimate slightly exceeds the pre-set bioequivalence upper limit of 125% on Day 8 and it is within the upper limit on Day 10.

4. Adverse Events

Safety Results

Following, a resume of the safety results obtained during the study:

- Overall, 92 treatment-emergent adverse events (TEAEs) were experienced by all the 24 (100%) study subjects. Specifically, 83.3% of subjects experienced at least one TEAE after co-administration of DEXA and NEPA FDC and 70.8% of subjects after administration of DEXA alone;
- the Investigator deemed 35 of the 92 reported TEAEs as related to NEPA FDC and 82 of the 92 reported TEAEs as related to dexamethasone. TEAEs related to NEPA FDC occurred at a frequency of 62.5% (15 out of 24 subjects), while TEAEs related to DEXA occurred at an overall frequency of 100% (all the 24 subjects included in the safety analysis);
- the most frequent (>20%) TEAEs related to NEPA FDC were hiccups with an overall frequency of 45.8%, followed by constipation whose overall frequency was 33.3%. All occurrences of both events had a mild intensity and were transient in nature. Both burdens are known and expected untoward effects of netupitant/palonosetron;
- the most frequent (>20%) TEAEs related to dexamethasone was an elevation in leukocytes, with an overall frequency of 95.8%, followed by an elevation in neutrophils, whose overall frequency was 87.5% and by hiccups with an overall frequency of 45.8%. Leukocytosis of moderate intensity is a known and expected untoward effect of dexamethasone. The Investigator judged the abnormal leukocyte values as unlikely related to NEPA FDC, but probably related to dexamethasone;
- no other clinically significant (CS) abnormality was found for any laboratory parameter;
- no serious adverse event (SAE) occurred during the study;
- no severe AEs were reported;
- no subject discontinued the study due to AEs or safety reasons;
- no CS change in vital signs, body weight (BW) or ECGs was observed during the study.