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Overcoming Drug Development Challenges with Nanotechnology:

Positive data from a first-in-human trial with a nanoformed drug

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Quotient Sciences

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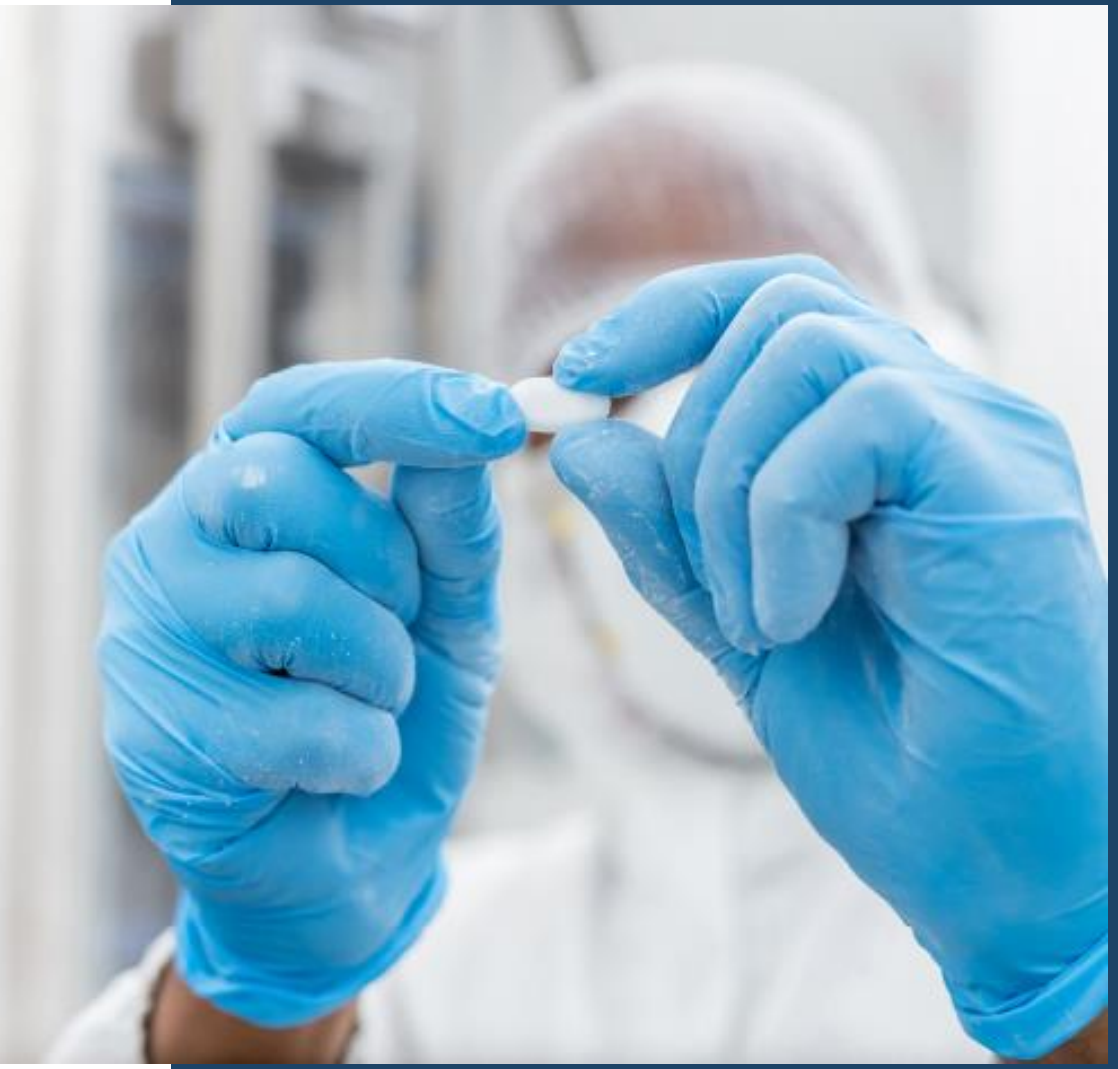
Overview

- Study background, objectives and design
- Study data
- Discussion and study outcome



Study Background and Objectives

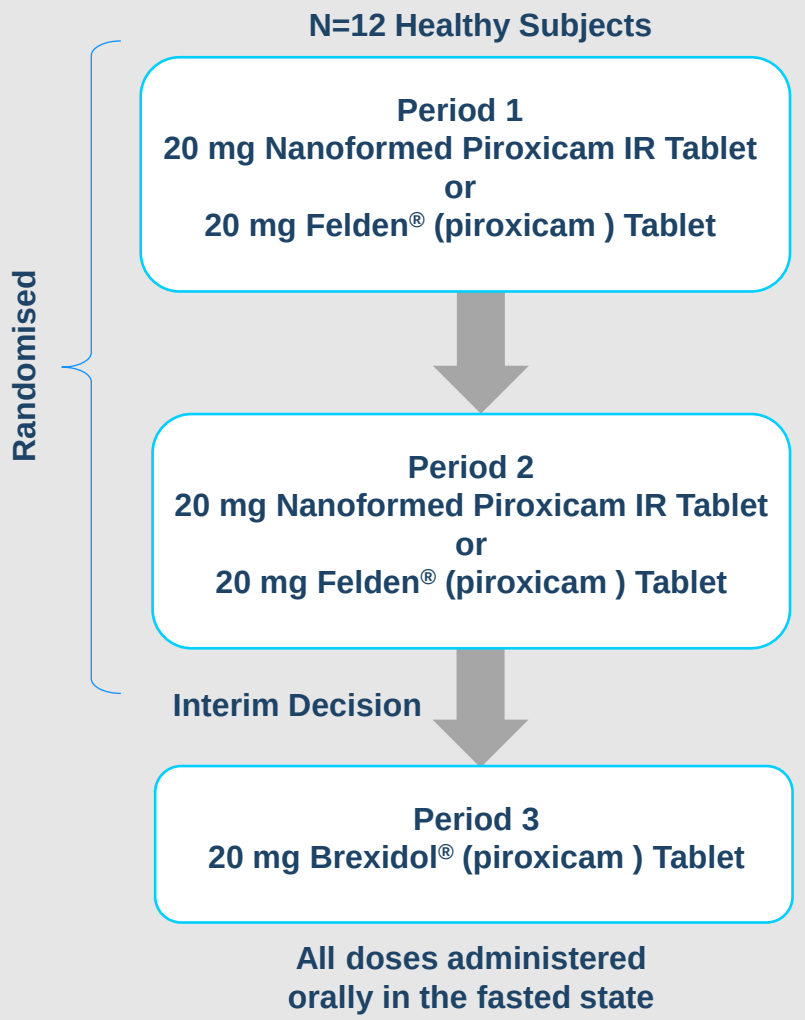
- **This study was a Phase 1, single-centre, open-label, partially-randomised pharmacokinetic (PK) evaluation of a nanoformed oral immediate release (IR) piroxicam tablet in up to 3 periods in healthy subjects**
  - Piroxicam, a commercially available drug with poor aqueous solubility / dissolution-rate limited oral absorption, selected as a model compound to demonstrate potential benefits of nanonisation in improving solubility, dissolution and in vivo absorption

- **Primary Objective**
  - To determine the PK and relative bioavailability of piroxicam following administration of 20 mg single oral doses of Nanoformed Piroxicam Immediate Release (IR) Tablets and Felden® (piroxicam) Tablets (reference) in healthy subjects in the fasted state
- **Secondary Objective**
  - To provide additional safety and tolerability information for piroxicam following administration of single oral doses of 20 mg Nanoformed Piroxicam IR Tablets in healthy subjects
- **Exploratory Objective**
  - To determine the PK and relative bioavailability of piroxicam following administration of 20 mg single oral doses of Nanoformed piroxicam IR tablet, and Brexidol® (piroxicam) Tablets (alternative reference) in healthy subjects in the fasted state

- **The study was performed at Quotient Sciences using a Translational Pharmaceutics platform where drug product manufacturing was integrated with clinical testing in real time**

Study Design

- Nanoformed Piroxicam IR Tablet 20 mg drug product was developed and approved within the Investigational Medicinal Product Dossier (IMPD)
- Period 3 was an optional study period used to incorporate an alternative piroxicam reference tablet (20mg Brexidol®) in the fasted state
- An interim decision meeting following Period 2 reviewed emerging PK and safety data and confirmed Period 3 execution and the selected product and prandial state
- Subjects were retrospectively stratified by CYP2C9 phenotype, the main metabolising enzyme for piroxicam, with 7 normal and 5 intermediate metabolisers identified



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Study Data

PK Data

- Following 20 mg single oral administration of Nanoformed Piroxicam IR Tablets, Felden® Tablets or Brexidol® Tablets, piroxicam concentrations were evident by 0.25 h indicating rapid absorption
- Median Tmax for Felden® and Brexidol® occurred between 2.25 h and 2.75 h post dose, whilst the Nanoformed Piroxicam IR Tablets, resulted in a reduction in median Tmax to 1.75 h

Table 1. Piroxicam Geometric Mean (Geometric CV%) Plasma PK Parameters

Dose IMP Status	20 mg Nanoformed Piroxicam IR Tablet Fasted	20 mg Felden® (piroxicam) Tablet (reference) Fasted	20 mg Brexidol® (piroxicam) Tablet (alternative reference) Fasted
Tmax (h)	1.750 (0.75-4.00)	2.750 (0.75-12.00)	2.250 (0.50-8.00)
Cmax (ng/mL)	2230 (15.6)	2230 (18.8)	2300 (17.1)
AUC(0-1) (ng.h/mL)	1150 (39.3)	863 (49.1)	1180 (31.9)
AUC(0-24) (ng.h/mL)	36200 (10.8)	38200 (13.0)	39900 (12.5)
AUC(0-last) (ng.h/mL)	83600 (16.9)	85900 (14.1)	92000 (14.7)
T1/2 (h)	50.685 (47.9) [n=6]	54.193 (41.4) [n=5]	56.366 (42.5) [n=7]

Figure 1a. Geometric Mean Plasma Piroxicam Concentration vs Time Profiles

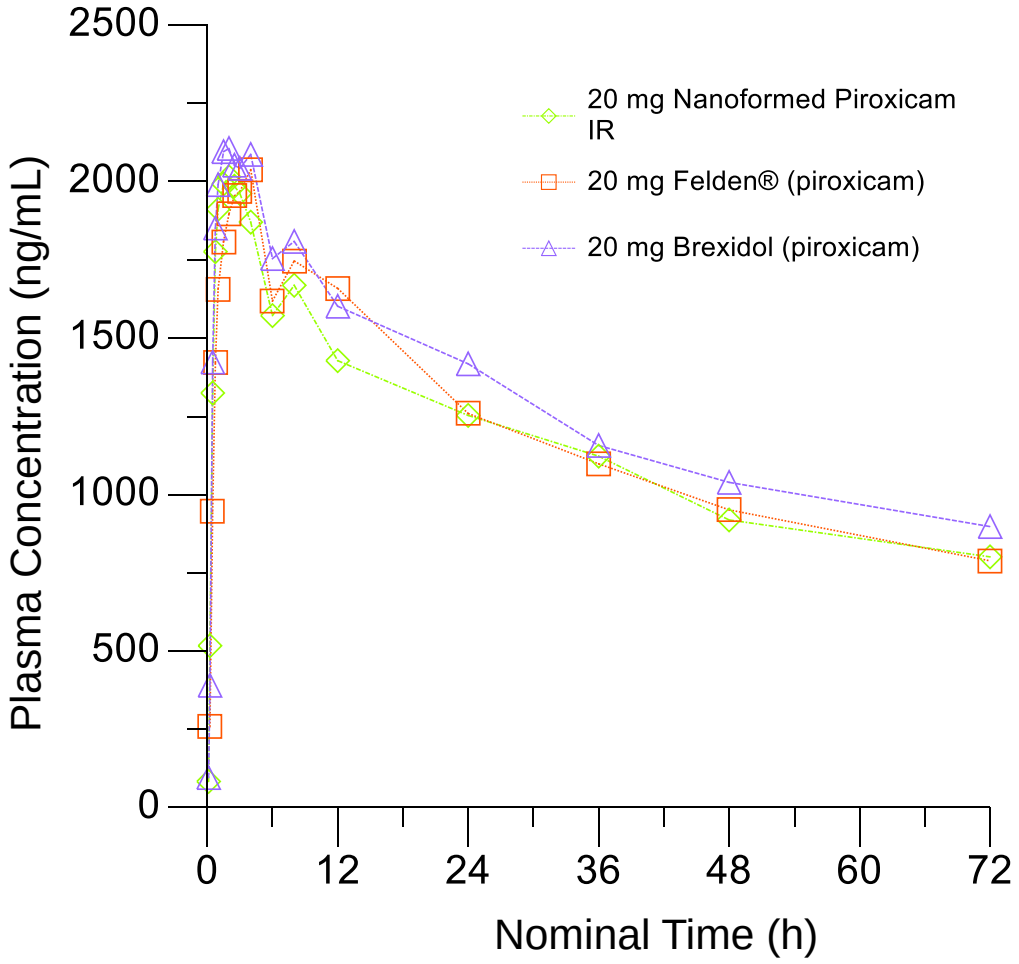

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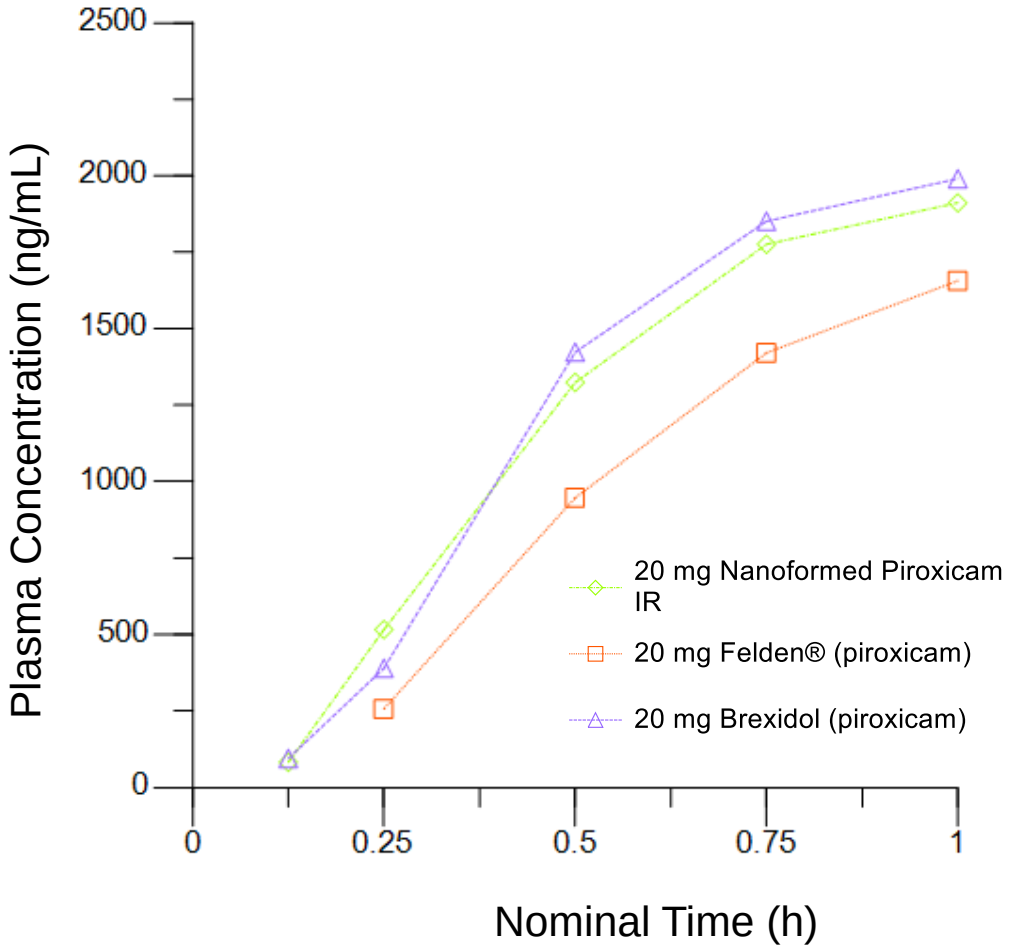
Figure 1b. Geometric Mean Plasma Piroxicam Concentration vs Time Profiles

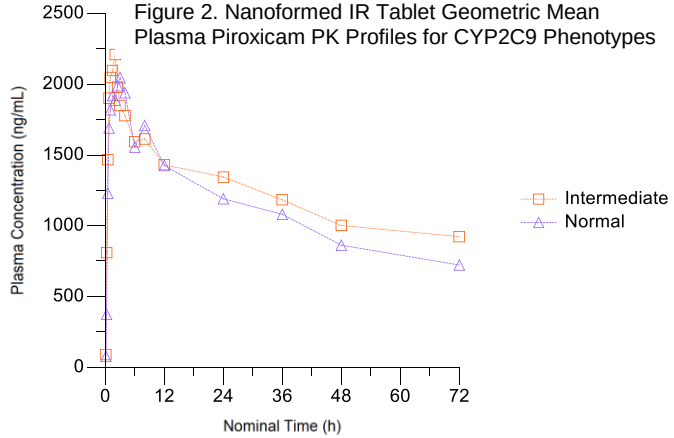


PK Data (2)

Formal statistics:

- Tmax for Nanoformed Piroxicam IR Tablets significantly earlier (~ 0.9 h) than Felden® Tablets; no significant difference compared to Brexidol® Tablets
- Plasma exposure for Nanoformed Piroxicam IR Tablets similar for Cmax, AUC(0-24) and AUC(0-last), while AUC(0-1) showed a statistically significant increase of 33%, compared with Felden® Tablets
- Cmax and AUC(0-1) plasma exposures for Nanoformed Piroxicam IR Tablets similar to Brexidol® Tablets. AUC(0-24) and AUC(0-last) exposure for Nanoformed Piroxicam IR Tablets was slightly less (approximately 9%) than Brexidol® Tablets, the difference was statistically significant. Using the relevant bioequivalent guidance documents there is evidence that the two formulations could be considered similar in terms of PK exposure levels, however this was not the purpose of this study.
- CYP2C9 intermediate (n = 5) or normal (n = 7) metabolisers in the study, showed no notable difference in geometric mean PK parameters, however, slight increases in AUC(0-last) and mean plasma half-life values for intermediates in comparison to normal was broadly aligned with expectations

Figure 2. Nanoformed IR Tablet Geometric Mean Plasma Piroxicam PK Profiles for CYP2C9 Phenotypes



Safety Data

- There were no severe or serious Adverse Events (AEs), deaths or AEs leading to withdrawal from the study
- 20 mg Nanoformed Piroxicam IR Tablets were well tolerated in 12 healthy subjects, with no Treatment Emergent Adverse Events (TEAEs) reported, compared with 2 and 1 subjects reporting 3 and 1 events for 20 mg Felden® and 20 mg Brexidol®, respectively
- One subject reported the AE of rash assessed as possibly related to drug product following 20 mg Felden®. No treatment was required with spontaneous resolution after around 5 days and no recurrence following administration of Nanoformed Piroxicam IR Tablets and Brexidol® Tablets, respectively. All other AEs were assessed as unrelated to IMP
- No clinically relevant changes in safety laboratory analysis, vital signs, ECGs or physical examination findings
- One subject required concomitant medication during the trial – local anaesthetic use for the unrelated AE of dental filling
- There were no severe or serious AEs, deaths or AEs leading to withdrawal from the study and Nanoformed Piroxicam IR Tablets were well tolerated in 12 healthy subjects at a dose of 20 mg, with no TEAEs reported

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Discussion and Study Outcome

Discussion

- The significant increase in AUC(0-1) between Nanoformed Piroxicam IR Tablets and Felden® Tablets suggests the potential for more rapid onset of analgesic action whilst the slight differences in overall exposure between Nanoformed Piroxicam IR Tablets and reference products would not be expected to have a clinical impact

- 20 mg Nanoformed Piroxicam IR Tablets demonstrated a Tmax earlier than both the 20 mg Felden® and 20 mg Brexidol®, with the median value being significantly lower than Felden®

- Nanoformed Piroxicam IR Tablet was formulated using traditional excipients and the formulation approach resembled that used in Felden®. Brexidol® incorporates beta-cyclodextrin as a formulation excipient to enhance piroxicam solubility through complexation, with rapid absorption for this reference expected in vivo. The slightly faster absorption observed for the Nanoformed Piroxicam IR Tablets compared to Brexidol® shows that the CESS® drug substance nanoforming process can be an alternative to complex formulation approaches such as those using cyclodextrins. This offers the potential for improved performance without the need for additional excipients. Thus, nanoforming can enable higher drugs loads compared to more complex formulations with high amounts of excipients needed

- Peak plasma concentration variability was observed to be slightly lower for 20 mg Nanoformed Piroxicam IR Tablets than both reference products. This may be due to a more uniform and reproducible total surface area for nanoformed piroxicam drug particles facilitating a more uniform dissolution and subsequent absorption and could offer benefits in reducing downstream response variation

Study Outcome

- The study primary and secondary objectives were met, in addition to the exploratory objective related to a comparison of the Nanoformed Piroxicam IR Tablet with Brexidol® as an alternative reference product
- The study results show that Nanoform's CESS® process enabled development of a fast-acting piroxicam immediate release tablet formulation with increased dissolution rate, more rapid absorption and improved drug delivery performance in comparison to a standard reference piroxicam IR tablet
- In addition, the study results indicate that nanoforming can be used as an alternative to complex formulation approaches with the potential for improved performance without the need for additional excipients
- The study outcomes support the clinical utility of this formulation technology and its potential applicability in producing fast-acting dosage forms for poorly soluble drugs, such as piroxicam

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