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Pharmacokinetic equivalence observed between an emulsion formulation of vinorelbine (ANX-530) and vinorelbine solution in a clinical study of patients with advanced cancer.

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Abstract:

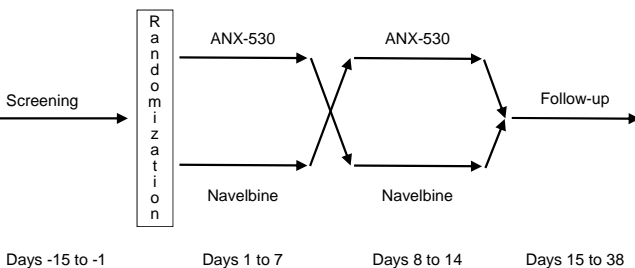
Background: An oil-in-water emulsion formulation of vinorelbine, ANX-530, was evaluated for bioequivalence with vinorelbine solution in a multi-center, open-label, randomized, crossover study. Vinorelbine is a semisynthetic derivative of vinblastine and is approved for use in patients with non-small cell lung cancer. However, vinorelbine solution is a vesicant and venous irritant, and these adverse effects can limit its tolerability. Preclinical studies demonstrated less venous irritation for ANX-530 while demonstrating equivalent antitumor activity and similar pharmacokinetic profiles for ANX-530 and vinorelbine solution.

Methods: A clinical study was performed to determine the bioequivalence of ANX-530 and vinorelbine solution. The bioequivalence study enrolled cancer patients in a standard 2-period crossover design randomized for sequence. Patients were eligible with an advanced cancer potentially sensitive to vinorelbine after failure of standard treatments for the tumor. Patients requiring concomitant chemotherapeutic agents or having prior vinorelbine or mitomycin treatment were excluded. Patients were randomly assigned to receive a single intravenous dose of either ANX-530 or vinorelbine solution in the first study period, then 1 week later crossover to the other vinorelbine formulation. All drug administrations were given as 10-minute infusions at a dose of 30 mg/m². Blood samples for pharmacokinetic analysis were collected predose, 10, 20, and 40 min, and 1, 3, 6, 24, 48, 72, and 144 hr after the end of the infusion. Hematology, serum chemistry, and adverse event reporting were performed throughout the study period. The primary endpoint of pharmacokinetic equivalence was assessed by analysis of variance comparison of the log transformed values of vinorelbine area under the curve (AUC) and maximum plasma concentration (C_{max}).

Results: A total of 31 patients were enrolled. The median age was 60 years (range 31-83), and 26 patients (84%) were female. 20 patients (65%) had breast cancer, 3 patients (10%) had lung cancer, and 8 patients (26%) had other cancer types. All patients had been previously treated with chemotherapy. All 31 patients received both formulations and had adequate pharmacokinetic data. The geometric mean ratio percentage (90% confidence interval) of C_{max} was 104% (87% - 123%), of AUC_{last} was 106% (99% - 112%), and of AUC_{inf} was 106% (100% - 112%).

Conclusion: The 90% confidence intervals of the ratio for C_{max} and AUC parameters were within the 80-125% predefined interval for bioequivalence based on FDA guidelines. As such, pharmacokinetic equivalence was observed between ANX-530 and vinorelbine solution.

Study Schema:



Patients and Methods:

Objectives

Primary Objective: To demonstrate the pharmacokinetic equivalence of ANX-530 and the Reference Product, Navelbine[®] (vinorelbine solution).

Secondary Objective: To determine the safety of a single dose of ANX-530.

Eligibility

Adult patients with advanced cancer potentially sensitive to vinorelbine, and who failed to respond to standard treatment were eligible if they had life expectancy of at least 3 months; had adequate performance status; and had adequate hematology and serum chemistry parameters.

Patients were not eligible if they had received previous treatment with vinorelbine or mitomycin; any history suggesting or demonstrating resistance to, lack of response to, or intolerance of any prior vinca alkaloid treatment; active infection; anticancer therapy completed within 4 weeks prior to the first day of study treatment; participated in another experimental drug study within 4 weeks prior to the first day of study treatment; or required any concomitant chemotherapeutic agent other than the study medication.

Treatment

Patients were randomly assigned to receive either a single intravenous dose of 30 mg/m² of ANX-530 or 30 mg/m² of Navelbine in the first study period. One week later, patients crossed over to the other vinorelbine formulation.

Patient Demographics:

Patients were enrolled in 7 sites in Argentina. Patients were randomized to treatment sequence: ANX-530 followed by Navelbine, n=16; Navelbine followed by ANX-530, n=15. Patients in both treatment sequence groups had similar baseline demographic characteristics with no clinically relevant differences.

Table 1: Patient Demographics

Characteristic	N (%)
Total enrolled	N=31
Bioequivalence population	31 (100%)
Safety population	31 (100%)
Gender	
Male	5 (16%)
Female	26 (84%)
Age	
18 - 65	20 (65%)
≥ 65	11 (35%)
Race	
White	26 (84%)
American Indian or Alaskan Native	5 (16%)
Ethnicity	
Hispanic or Latino	31 (100%)
Not Hispanic or Latino	0 (0%)

Table 2: Patient Cancer History

Characteristic	N (%)
Cancer type	
Breast	20 (65%)
Lung	3 (10%)
Lymphoma	2 (6%)
Squamous cell vulva	1 (3%)
Other	5 (16%)
Metastatic site (patient may have more than 1 category)	
Lymph node	16 (52%)
Bone	8 (26%)
Lung	7 (23%)
Soft tissue	5 (16%)
Liver	3 (10%)
Pleural cavity	3 (10%)
Peritoneum	2 (6%)
Other	5 (16%)

Pharmacokinetic Results:

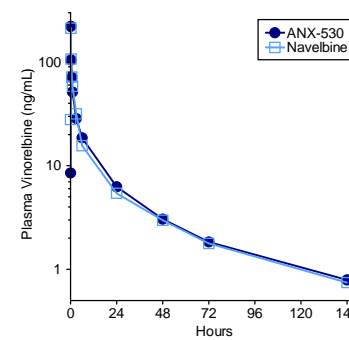


Figure 1: Mean Concentration-Time Profiles

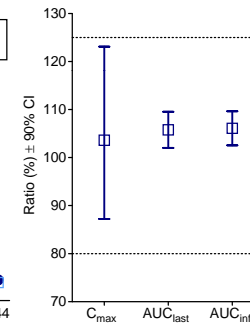


Figure 2: Pharmacokinetic Equivalence between ANX-530 and Navelbine

The variability in the ANOVA analysis for AUC was low. The variability in the ANOVA analysis for C_{max} was higher than the variability in AUC. Generally, the high C_{max} values occurred after just one of the treatments with the other treatment in the same patient having a C_{max} in the 100-300 ng/mL range. Incidences of high C_{max} values were observed in both treatments and in both periods.

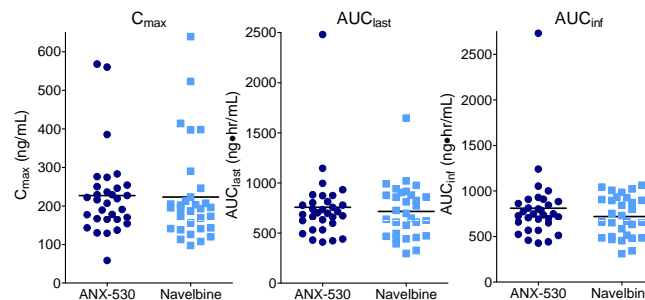


Figure 3: Individual Pharmacokinetic Parameters

The pharmacokinetic parameters were determined using WinNonLin software using actual collection times. Log transformed parameters of C_{max}, AUC_{last}, and AUC_{inf} were analyzed using an ANOVA model with factors for treatment (ANX-530 versus Navelbine), period (Days 1-7 versus Days 8-14), sequence (ANX-530 followed by Navelbine versus Navelbine followed by ANX-530), and patient within sequence.

Table 4: Pharmacokinetic Parameters

Parameter	ANX-530 (mean ± SD)	Navelbine (mean ± SD)	Geo. Mean Ratio (%)	90% CI	Acceptable Range
C _{max} (ng/mL)	227 ± 108	223 ± 125	104	87 - 123	80 - 125
AUC _{last} (hr·ng/mL)	758 ± 364	717 ± 272	106	99 - 112	80 - 125
AUC _{inf} (hr·ng/mL)	810 ± 400	719 ± 223	106	100 - 112	80 - 125
T _{max} * (hr)	0.33 (0-0.83)	0.33 (0-0.5)			
t _{1/2} (hr)	46.5 ± 12.4	40.5 ± 13.5			
T _{last} * (hr)	144 (72-144)	144 (72-144)			

* T_{max} and T_{last} values = median (range)

Safety Results:

ANX-530 was well-tolerated in patients with advanced cancer. The incidence of AEs was similar between the ANX-530 and Navelbine treatment and was as expected with vinorelbine treatment.

The AE profile between ANX-530 and Navelbine treatment was similar in terms of relatedness and severity assessments, except for AEs involving General Disorders and Administration Site Conditions. In particular, post-hoc analysis revealed statistically fewer infusion site reactions with ANX-530 treatment.

Table 5: Summary of Treatment-Emergent AEs by System Organ Class that Occurred in ≥3 Patients (≥10%)

System Organ Class	ANX-530 N=31	Navelbine N=31	P value
Patients Reporting At Least One Adverse Event	22 (71%)	25 (81%)	>0.05
Blood and Lymphatic System Disorders	15 (48%)	11 (35%)	>0.05
General Disorders and Administration Site Conditions	5 (16%)	14 (45%)	0.014
Gastrointestinal Disorders	11 (35%)	7 (23%)	>0.05
Infections and Infestations	3 (10%)	3 (10%)	>0.05
Musculoskeletal and Connective Tissue Disorders	4 (13%)	2 (6%)	>0.05
Respiratory, Thoracic, and Mediastinal Disorders	1 (3%)	3 (10%)	>0.05
Skin and Subcutaneous Tissue Disorders	3 (10%)	2 (6%)	>0.05

Conclusions:

ANX-530 and Navelbine were bioequivalent in a study population with advanced cancer potentially sensitive to vinorelbine.

The 90% confidence interval for comparing the exposure, based on C_{max}, AUC_{inf}, and AUC_{last} was within the accepted 80% to 125% limits, as recommended in FDA guidance.

The AE profile between ANX-530 and Navelbine was similar in terms of relatedness and severity assessments, except for AEs of General Disorders and Administration Site Conditions.

ANX-530 was well-tolerated with fewer infusion site reactions compared to Navelbine.