Pilot Bioavailability Study of a novel Bisphosphonate Osteotropic Drug Delivery System by oral route, for metastatic bone treatment

I.N.S.C.B. Institut Nord-Sud de Coopération Biopharmaceutique

3S Pharmacological Consultation & Research GmbH

Dr. Thierry Breul*, Stephanie Silva-Lejmi*, Dr Simona Rizea Savu**, Dr. Luigi Silvestro**

** Institut Nord Sud de Cooperation Biopharmaceutique, INSCB - CNRS, Montpellier, France - ** 3S Pharmacological Consultation & Research, GmbH, Harpsedt, Germany*

SUMMARY

Many oncology patients with breast, prostate, or other solid tumors get secondary metastases to bone. Current metastatic bone treatments are bisphosphonates by intravenous route with sales above $ 1 billion. There is therefore an unmet medical need for patients treated by regular infusions at hospitals / clinics as no oral formulation is available.
Bisphosphonates have very poor oral bioavailabilities, 0.6% in average. Design of drug delivery systems enhancing their oral absorption is therefore required for treatment efficiency

A novel Bisphophonate Osteotropic Drug Delivery System (BP-ODDS) was designed at INSCB to enhance oral absorption of bisphosphonates. A pilot bioavailability study comparing the novel BP-ODDS from INSCB with the currently marketed formulation of a bisphosphonate, was conducted on 12 fasting healthy volunteers, male and female, by 3S Pharmacological Consultation & Research GmbH.

Results obtained indicate that the novel BP-ODDS from INSCB is relevantly better absorbed from the gastrointestinal tract than the reference marketed formulation.

AUC of BP-ODDS formulation is 300 % higher than the one of reference product.

Cmax of BP-ODDS formulation is almost 500% higher than for the reference product

These results suggest that this novel Bisphosphonate Osteotropic Drug Delivery System (BP-ODDS) could be an answer to the unmet medical need of an oral formulation of bisphosphonate for metastatic bone treatment.

BACKGROUND

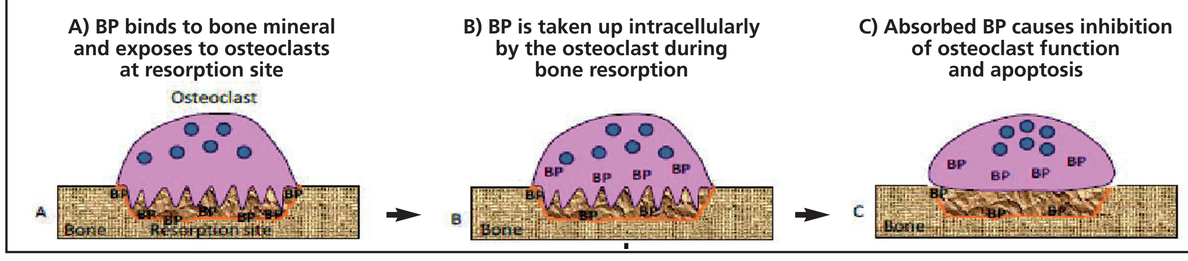
Most bone metastases are characterized by excess osteoclast number and activity. Some bisphosphonates, potent inhibitors of osteoclast activity, are widely used for prevention of bone metastases and to treat cancer-induced bone diseases in a range of solid tumors, hypercalcemia of malignancy and multiple myeloma.
Bisphosphonates also inhibit tumor proliferation by depriving tumor of growth factors released during osteolysis. *In vitro*, bisphosphonates induce cell death and/or cytostasis in prostate cancer cell lines and inhibit tumor cell adhesion, migration and invasion.

Currently, bisphophonates for cancer therapies are administered intravenously by slow infusion.

Infusion of bisphosphonates is associated with dose and infusion rate dependent effects on renal function. High bisphosphonate doses can cause severe renal toxicity unless infused slowly over many hours. Oral administration, on the other hand, is complicated by poor bioavailability (< 1 % in humans) and poor gastrointestinal tolerability.

This has limited their use in oncological therapies to intravenous infusion to achieve the doses required for efficacy.

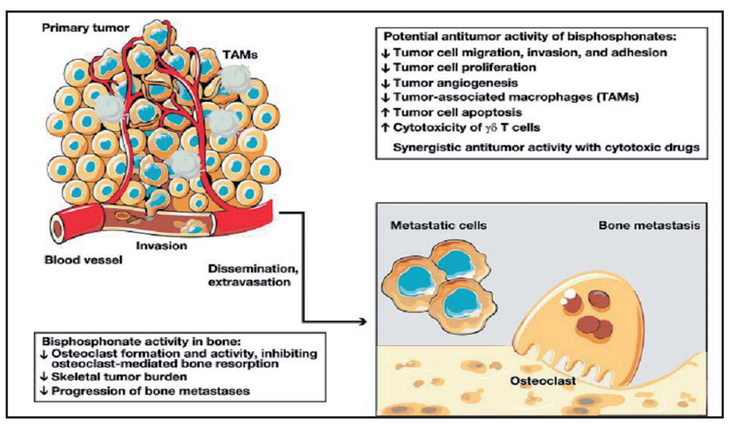
Mechanism of action of Bisphosphonates



INTRODUCTION

The purpose of the study was to preliminary assess the relative bioavailability by oral route of a novel Bisphosphonate Osteotropic Drug Delivery System (BP-ODDS), following a 35 mg single oral dose, versus an equal dose of reference marketed formulation, Actonel 35 mg ®, all administered to fasting healthy volunteers.
The comparative bioavailability assessment was based on plasma drug levels of the test bisphosphonate : sodium risedronate.

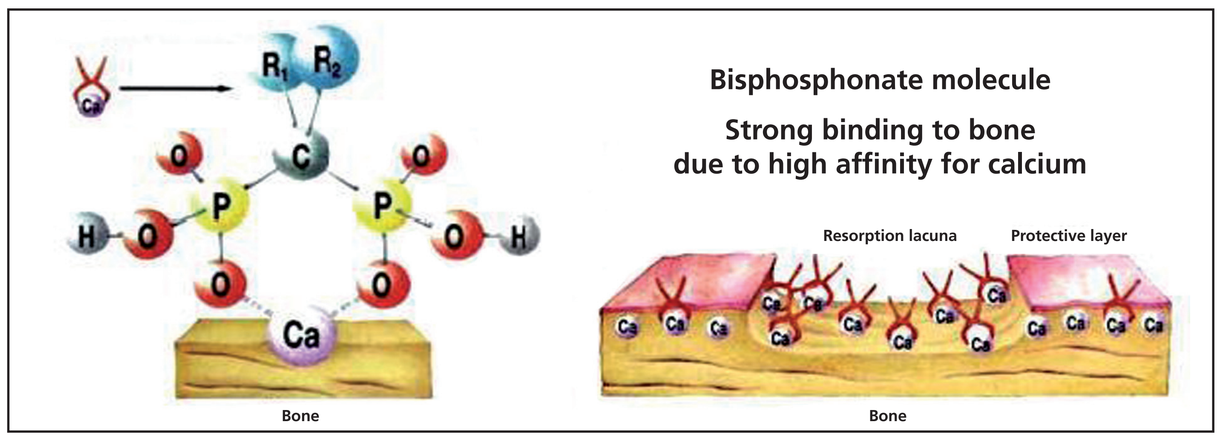
The novel Bisphosphonate Osteotropic Drug Delivery System (BP-ODDS) evaluated was developed by Institut Nord Sud de Coopération Biopharmaceutique (INSCB / CNRS Montpellier, France) to improve bisphosphonates oral bioavailability and gastrointestinal tolerability, and thereby enabling the development of oral dosage forms for oncology indications.



INSCB BISPHOSPHONATE OSTEOTROPIC DRUG DELIVERY SYSTEM (BP-ODDS)

The BP-ODDS developed is based on a INSCB proprietary technology combining both effects of two excipients, one intestinal penetration enhancer and one calcium chelatant agent, both registered at pharmacopeias and authorized for oral administration. Manufacturing process is a classical physical mixture of excipients system and drug substance.
The new formulation can be processed in a film coated tablet form or in hard gelatin capsules, and shows no degradation of the active drug after one year stability. BP-ODDS was also designed to overcome bisphosphonates precipitation in presence of divalent cations, thus increasing their solubilities in physiological fluids.

This Osteotropic Drug Delivery System (BP-ODDS) has been patented by INSCB in 2011



PILOT COMPARATIVE BIOAVAILABILITY STUDY DESIGN

Methodology: Two period, two sequence, cross-over, block randomized pilot study on healthy volunteers in fasting conditions. Hospitalization of subjects until 24 hours post administration.

Products administered:
TEST : one film-coated tablet of 35 mg Sodium Risedronate formulation of I.N.S.C.B – CNRS, Montpellier, France;
REFERENCE : one film-coated tablet of 35 mg, ACTONEL® from Procter & Gamble Pharmaceuticals GmbH.

Blood samplings: collected before dose (0.0) and at 0.25, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 48.0 and 168.0 hours post dose, after each administration.

Washout period : 46 days.

Analytical method: Determination of Risedronate in plasma by HPLC- MS/MS.

Pharmacokinetic parameters: AUC0-t , Cmax, AUC O-inf , Tmax, % extrapolated AUC, T1/2 , MRT.

Number of subjects: 12 enrolled and analysed

Diagnosis and selection criteria: Male & female, healthy volunteers, aged 18-45, body mass index within 19 - 27.5

Dose and mode of administration: per os one film-coated tablet of 35 mg with 200 ml of low carbonated water.

Duration of treatment: One day per period

Criteria for Evaluation: Risedronate Cmax, AUC 0-t, AUC O-inf (as primary); T max (as secondary); Risedronate % extra AUC, MRT, T half (as additional).

Safety: Laboratorv data / Vital signs / Adverse events

Statistical methods: Cmax, AUC 0-inf and AUC 0-t, ANOVA after logarithmic transformation, classic 90% confidence intervals for the intra-individual ratios and Schuirmann two one-sided parametric T-test. Tmax: Wilcoxon Signed-Rank Test. MRT, T half: ANOVA test
Descriptive statistics: arithmetic mean, geometric mean, SEM, standard deviation, median, range.

RESULTS

Pharmacokinetics parameters :
Parmacokinetics of risedronic acid : REFERENCE : Actonel® TEST : BP-ODDS / INSCB.

Reference treatment : Actonel ® 35 mg

	Cmax (pg/ml)	Tmax (hours)	AUC 0-t (pg/ml*h)	AUC 0-inf (pg/ml*h)	AUC % extra (%)	T HALF (hours)	MRT (hours)
Mean	21397.039	0.708	68828.104	316574.414	23.205	132.793	183.415
SD	18321.720	0.298	65124.464	803333.083	27.070	358.407	519.256
CV	85.627	42.121	94.619	253.758	116.653	269.900	283.104

Test treatment : BP-ODDS / INSCB Risedronate 35 mg

	Cmax (pg/ml)	Tmax (hours)	AUC 0-t (pg/ml*h)	AUC 0-inf (pg/ml*h)	AUC % extra (%)	T HALF (hours)	MRT (hours)
Mean	103773.408	0.375	218333.543	241367.124	9.419	50.064	37.736
SD	70151.856	0.131	175121.887	232037.248	11.888	69.712	63.163
CV	67.601	34.816	80.208	96.135	126.202	139.245	167.381

Comparative bioavailability of the primary parameters (test name : Classic 90% CI) :

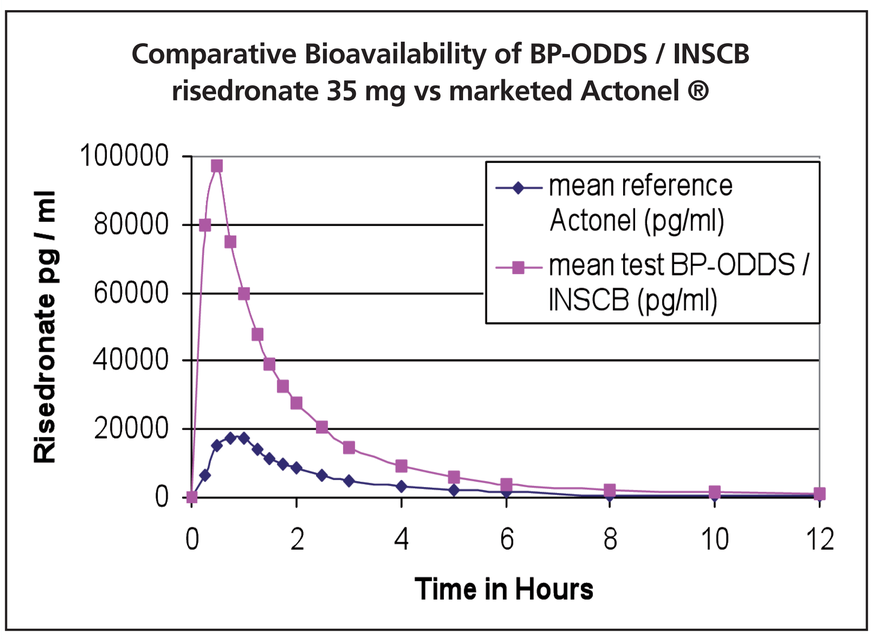
Parameter	AUC 0-t	AUC 0-inf	C max	T max
Test Value (Test / Reference)	295.854	266.363	480.004	0.530

Comparative coefficients of variation (CV) of the primary pharmacokinetic parameters

Parameter	AUC 0-t	AUC 0-inf	C max
Test Value (CV Test / CV Reference)	0.85	0.38	0.79

SAFETY : no serious adverse events.

CONCLUSION



1. **Test product : BP-ODDS / INSCB Sodium Risedronate 35 mg film-coated tablets, is better absorbed from the gastrointestinatl tract than REFERENCE, ACTONEL® 35 mg.**

   AUC of BP-ODDS is 300 % higher

   C max of BP-ODDS is 500 % higher

2. **T max of BP-ODDS is half of T max obtained with REFERENCE product Actonel®, indicating**

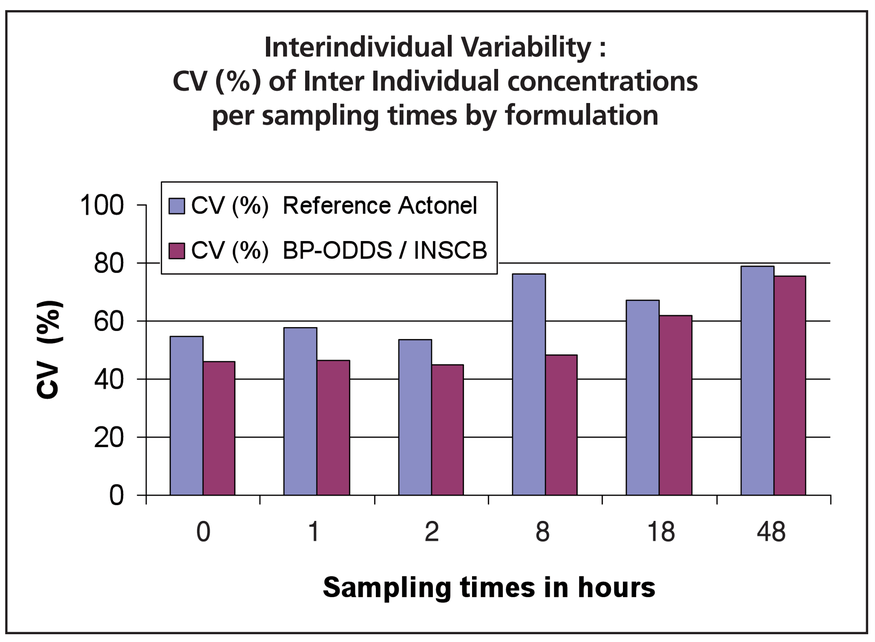
   a twice quicker efficiency for BP-ODDS.

3. **Variability of primary pharmacokinetic parameters of BP-ODDS is lower than REFERENCE Actonel®**

   Variability : 20 % lower for C max
   60% lower for AUC 0-inf

4. **BP-ODDS test treatment safety :**

   very well tolerated after oral single dose.



The film coated tablet of Bisphosphonate Osteotropic Drug Delivery System (BP-ODDS) developed by INSCB is supra-bioavailable when compared to the reference marketed product Actonel® with a factor ranging from 300 % for the AUC to a factor of almost 500 % for C max.

BP-ODDS tablets or capsules offer an alternative route of administration to bisphosphonate products currently marketed, covering an unmet need for oral bisphosphonates in oncology. BP-ODDS is an effective and potentially safer alternative to bisphosphonate intravenous infusions which could offer the following advantages :

Improved quality of life for the patient • Flexibility in the dosing regimen • Improved compliance