Tissue distribution of EDP-305, a highly selective and potent FXR agonist, in preclinical species

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ABSTRACT

Background: EDP-305, a selective and potent small molecule Farnesoid X receptor (FXR) agonist, is currently being developed for the treatment of non-alcoholic steatohepatitis (NASH) and primary biliary cholangitis (PBC). Herein, we report the tissue distribution of EDP-305 in preclinical species. **Methods:** Male C57BL/6 mice, male and female CD-1 mice were administered with a single oral dose of radioactive-labeled [^{14}C]EDP-305 at 10 mg/kg (100 µCi/kg) formulated in 0.5% methylcellulose in deionized water. The [^{14}C]EDP-305 concentrations in fifty-seven (57) tissues were determined using validated quantitative whole body autoradiography (QWBA). Pharmacokinetic parameters in plasma and tissue samples were calculated by non-compartmental analysis using Phoenix® WinNonlin® software. **Results:** [^{14}C]EDP-305 was well absorbed in male C57BL/6 mice and male and female CD-1 mice, regardless of strain and sex. Tissues with the highest [^{14}C]EDP-305 exposure were small intestine, liver and gall bladder, with tissue-to-plasma exposure ratios of 69.9, 10.7 and 10.5, respectively. All the other fifty-four (54) tissues tested had less exposure than plasma. Very little radioactivity was found in melanin-containing tissues (e.g., skin and ocular system) and the central nervous system. High exposure in gall bladder suggested that biliary excretion was a major elimination pathway for EDP-305. The concentrations in all of the tissues were similar between male and female mice. Areas under the curve (AUC) in plasma, small intestine and liver were 50, 536 and 3,513 µg equivalent-hr/mL, respectively, with long half-lives of 6, 27 and 45 hours. Plasma, small intestine and liver had [^{14}C]EDP-305 concentrations of 0.24, 1.34 and 35.7 µg equivalent/mL, respectively, at 24 hours post dose, which was consistent with the observed long half-lives in these tissues. **Conclusions:** EDP-305 preferentially penetrated into the liver and small intestine, two NASH target organs, with sustained pharmacokinetic exposure. Current data makes EDP-305 attractive for further investigation in NASH.

INTRODUCTION

- EDP-305, a selective and potent small molecule Farnesoid X receptor (FXR) agonist, is currently being developed for the treatment of non-alcoholic steatohepatitis (NASH) and primary biliary cholangitis (PBC).
- The purpose of this study was to assess the tissue distribution of radioactivity in the male C57BL/6 mice, male and female CD-1 mice following a single oral gavage administration of [^{14}C]-EDP-305 using QWBA.

METHODS

Study Design

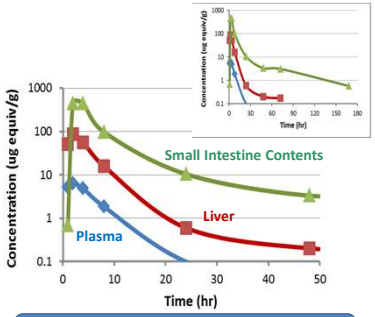
Group	Study Design	# Animals/ Gender - Type	Dose Level mg/kg	µCi/kg	mL/kg	Collection Matrices and Time Points/Intervals Post-Dose
1	Tissue Distribution	8M C57BL/6	10	100	10	Blood/plasma and carcass: 1, 2, 4, 8, 24, 48, 72 & 168 hours
2	Tissue Distribution	5 M / 5 F CD-1	10	100	10	Blood/plasma and carcass: 1, 4, 8, 24 & 168 hours

Tissues and Areas of Interest

Adrenal gland	Intra-orbital lachrymal gland	Prostate (male only)
Adrenal cortex	Kidney	Salivary glands
Adrenal medulla	Kidney cortex	Seminal vesicle (male only)
Aorta	Kidney medulla	Small intestine contents
Bile	Large intestine contents	Small intestine wall
Blood (cardiac)	Large intestine wall	Spinal cord
Bone (femur)	Lens	Spleen
Bone marrow (femur)	Liver	Stomach contents
Brain (whole)	Lung	Stomach wall (glandular)
Brown fat	Lymph node (cervical)	Stomach wall (non-glandular)
Caecum contents	Mammary gland region (female only)	Testis (male only)
Caecum mucosa	Muscle (femoral)	Thymus
Epididymis (male only)	Nasal turbinates	Thyroid gland
Esophagus wall	Non-pigmented skin (CD-1 only)	Trachea
Extra-orbital lachrymal gland	Oral mucosa	Urinary bladder contents
Eye	Ovaries (female only)	Urinary bladder wall
Gall bladder	Pancreas	Uterus (female only)
Harderian gland	Pigmented skin (C57BL/6 only)	Uveal tract
Heart	Pituitary gland	White fat (inguinal)

RESULTS

Tissue Distribution of [^{14}C]-EDP-305 in C57BL/6 Mice

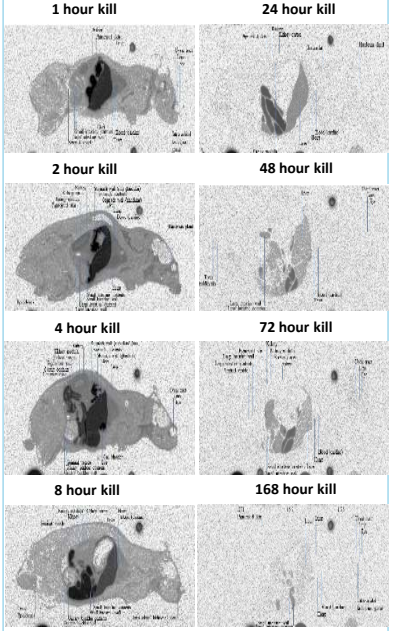


Key PK Parameters of [^{14}C]-EDP-305 in C57BL/6 Mice

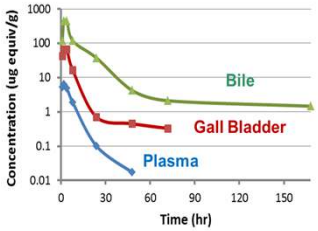
Tissue	C_{max} (µg/g)	$T_{1/2}$ (hr)	$AUC_{0-\infty}$ (µg-hr/g)	AUC Tissue: Plasma Ratio
Plasma	6.40	6.10	50.26	
Liver	86.40	27.24	536.54	10.7
Small Intestine Contents	446.00	45.02	3513.01	69.9

RESULTS

Time-course Whole-body Autoradiograms of Male C57BL/6 Mice



Tissue Distribution of [^{14}C]-EDP-305 in C57BL/6 Mice

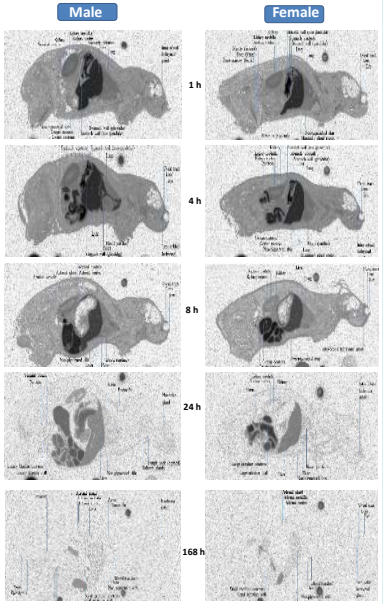


Key PK Parameters of [^{14}C]-EDP-305 in C57BL/6 Mice

Tissue	C_{max} (µg/g)	$T_{1/2}$ (hr)	$AUC_{0-\infty}$ (µg-hr/g)	AUC Tissue: Plasma Ratio
Plasma	6.40	6.10	50.26	
Gall Bladder	65.6	44.1	545	10.5
Bile	439	93.7	4496	85.9

RESULTS

Time-course Whole-body Autoradiograms of CD-1 Mice



CONCLUSIONS

- [^{14}C]-EDP-305 preferentially penetrated into the liver, gall bladder and small intestine.
- Very little radioactivity was found in the ocular and central nervous systems.
- Tissue distribution was similar between male and female.
- [^{14}C]-EDP-305-related material is not associating with melanin-containing tissues (e.g., skin and uveal tract).

ACKNOWLEDGEMENT

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