C. Toxicity

Preclinical animal toxicology studies were performed by Novo/Nordisk. These toxicology studies include acute toxicity study by oral administration to NMRI mice and Wistar rats, and acute toxicity study by intravenous administration to Wistar rats. In brief, clinical signs observed at low doses were expected due to the pharmacological properties of NNC-112 (D_1 antagonist) and included sedation or decreased locomotor activity. At higher doses of NNC-112, more severe locomotor signs such as ataxia and catalepsy were observed. In rats, decreased locomotor activity and sedation were observed in about half of the animals following a dose of 1 mg/kg i.v. The i.v. dose used in human studies ($\leq$ 6.54 µg) is thus 10,000 lower than the dose known to induce sedation in about half of the rats (1 mg/kg). Thus, no toxic effects are expected from injection of tracer doses of [^{11}C]NNC-112. A summary of these results are provided in the table below.

Study	Species	Route	Dose	Effects
1	NMRI mice	oral	6.25 to 1000 mg/kg, once	• Sings of toxicity were few and seen only after administration. • No NOEL found (no observed effects found in 7/10 at 6.25 mg/kg). • NOAEL found to be 6.25 mg/kg. • No change at necropsy. • LD_{50} found to exceed 100 mg/kg
2	Wistar rats	oral	6.25 to 500 mg/kg, once	• Sings of toxicity (decreased motor activity, catalepsy, shivering) were few and seen only after administration. • NOEL found to be 12.5 mg/kg. • NOAL found to be 25 mg/kg. • No change at necropsy. • LD_{50} found to exceed 500 mg/kg
3	Wistar rats	i.v.	1 to 18 mg/kg, once	• Treatment related signs related to pharmacological activity (depression and catalepsy) were limited to day of observation. • No NOEL found (No signs observed in 2/5 rats at 1 mg/kg). • NOAL found to be 1 mg/kg. • No change at necropsy. • LD_{50} found to be near 12 mg/kg.
4	Beagle dogs	oral	4 to 200 mg/kg, for four weeks	• Effects confined to clinical signs and related to pharmacological activity (sedation and ataxia) and blood chemistry. • No deaths occurred. • No changes in EKG and BP. • No treatment related changes in macroscopic pathology.
5	Salmonella Typhimurium	in vitro	5 to 500 µg per plate	• No mutagenic activity
6	Culture human lymphocytes	in vitro	2.5 to 25 µg/mL	• No evidence of toxicity at 2.5 µg/mL • Increase in aberrant cell frequencies at 2.5 µg/mL

NOEL = no observed event level.
NOAL = no observed adverse event level.

4) Oral administration to beagle dogs for four weeks.
5) Mutagenic potential (Ames test).
6) Clastogenic activity in cultured human lymphocytes.