Study type	**Species / Strain**	**Dose-level**	**Route**	**Endpoints evaluation**	**Significant findings**
MLA assay	L5178Y mouse lymphoma cells	0.24-50 µg/mL	*In vitro*	• Mutant frequency	• No statistically or biologically significant increases in the mutant frequency, without as well as with S9 metabolic activation.
Ames' test	Histidine-dependent strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA102)	Plate incorporation method 5.1-500 µg/plate Pre-incubation method 0.53-10 µg/plate	*In vitro*	• Revertant frequency	• No statistically or biologically significant increases in the revertant frequency using both methods, without as well as with S9 metabolic activation.
Micronuclei induction in the bone marrow	Rat/Wistar 5/sex/group	0, 20, 55, 150, 150 mg/kg b.i.d. 300 mg/kg s.i.d.	*Per os*	• Number of micronucleated polychromatic eythrocytes	• No biologically significant increases in the frequency of micronucleated polychromatic erythrocytes in the rat bone marrow.
Dose Range Finding 7-day repeated-dose (no follow-up)	Rat/Wistar 29 males/29 females 5/sex/group 3 satellites/sex for all treated-group	0, 20, 70, 100, 150, 250 mg/kg b.i.d.	*Per os*	• **A** • **B** • **C** • TKs	• Premature sacrifice of 1 female treated at 250 mg/kg on D6, due to poor clinical condition • Lower mean body weight gain at the highest dose-levels (150 & 250 mg/kg) • Hyperleukocytosis at the highest dose-levels (100 to 250 mg/kg) • Lower mean total protein, albumin and globulin levels at the highest dose-levels (100 to 250 mg/kg) • Dose-dependent increase of mean liver weight • Decreased mean spleen weight at 250 mg/kg • Dark foci in the glandular mucosa of stomach at 150 & 250 mg/kg

Study type	Species / Strain	Dose-level	Route	Endpoints evaluation	Significant findings
Dose Range Finding 7-day repeated-dose (no follow-up)	Rat/Wistar 13 males/13 females 5/sex/group 3 satellites/sex for treated-group	300 mg/kg s.i.d.	*Per os*	• **A** • **B** • **C** • PK	• Lower mean body weight gain associated with lower food consumption • Lower individual platelet count in males • Lower mean total protein, albumin in either gender and globulin levels (males only) • Increased mean liver weight • Dark foci in the glandular mucosa of stomach
Dose Range Finding 7-day repeated-dose (no follow-up)	Monkey/Cynomolgus 1 male/1female	1000, 1500 mg/kg b.i.d.	*Per os*	• **A** • **B** • TKs	• Vomiting and liquid feces, probably due to large volume administered • Slight body weight losses • Decreases of red blood cell counts, hemoglobin, packed cell volume & mean corpuscular volume • Increased APTT and prothrombin time • Decreased cholesterol and protein levels • Increased ASAT activity.
Dose Range Finding 7-day repeated-dose (no follow-up)	Monkey/Marmoset 3 males/3 females 1/sex/group	250 (1 day), 750 (1 day), 1000 (3 days) mg/kg b.i.d. 750 mg/kg b.i.d., 1500 mg/kg s.i.d. (7 days)	*Per os*	• **A** • **B** • **C** • TKs	• Vomiting at 1000 mg/kg b.i.d., occasional, dose-related vomiting with the other dose-levels. • Body weight loss for all dose-levels in all groups. • Increase in spleen and kidney weights & in serum urea in 1 female at the highest dose-level. • MTD = 750 mg/kg b.i.d. or 1500 mg/kg s.i.d.

Study type	Species / Strain	Dose-level	Route	Endpoints evaluation	Significant findings
Repeated-dose, 4 weeks (2 week follow-up)	Rat / Wistar 64 females/64 males 16/sex/group	20, 55, 150 mg/kg, b.i.d. 300 mg/kg s.i.d.	*Per os*	• **A** • **B** • **C** • Urine analysis • Histopathology • TKs	• Lower terminal body weights for dose-levels ≥ 55 mg/kg b.i.d. • Transient minimal to moderate histopathologic alterations in liver, Harderian gland, parotid salivary glands, stomach, thymus and pituitary gland • Adverse and transient changes in the female reproductive tract (lower ovaries and uterus weights at 150 mg/kg b.i.d. and 300 mg/kg s.i.d.) • All observations reversible or improved with cessation of treatment • NOAEL = 55 mg/kg b.i.d.
Repeated-dose, 4 weeks (3 week follow-up)	Monkeys/ Marmoset 25 females/25 males 5/sex/group	75, 250, 750 mg/kg, b.i.d. 1500 mg/kg s.i.d.	*Per os*	• **A** • **B** • **C** • Urine analysis • Ophtalmology • Cardiovascular investigations • Histopathology • TKs	• Frequent vomiting associated with SPL-464 treatment • Weight loss observed in non-treated and treated groups, consolidated by vomiting in treated group • Treatment stopped at day 10 for dose-levels ≥ 750 mg/kg and on day 18 for lower dose-levels due to poor clinical condition of animals, with sacrifice of 3 moribund animals at 750 mg/kg b.i.d. (day 9 and 14) and 2 moribund animals at 250 and 75 mg/kg b.i.d.(day 15). • Target organ: gastro-intestinal tract (reversible) • NOAEL = 250 mg/kg/day b.i.d.

Endpoints evaluation A:
- Clinical signs & mortality (daily)
- Body weight/ food consumption

Endpoints evaluation B:
- Haematology
- Serum clinical chemistry

Endpoints evaluation C:
- Necropsy & macroscopic examination
- Organ weight
- Sampling and preservation of all tissues