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First in Human, Single Ascending Dose Study in Healthy Volunteers of SNDX-6352, a Humanized IgG4 Monoclonal Antibody Targeting Colony Stimulating Factor-1 Receptor (CSF-1R)

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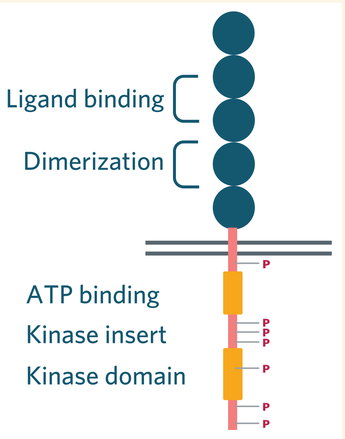
BACKGROUND

- Colony-stimulating factor-1 receptor (CSF-1R; **Figure 1**) is expressed on cells of the mononuclear phagocyte lineage
  - This includes immunosuppressive macrophages that accumulate within the tumor microenvironment
- These tumor-associated macrophages (TAMs) are believed to play a key role in inhibiting antitumor T-cell immune responses while promoting tumor progression[1]
- High levels of TAMs have been shown to correlate with poor prognosis for certain cancers[1]
- Preclinical studies have demonstrated that inhibition of TAMs can enhance antitumor immune response[2]
- SNDX-6352 is a humanized IgG4P monoclonal antibody with high-affinity binding for CSF-1R that is currently under investigation for the treatment of neoplastic diseases (**Figure 2**)

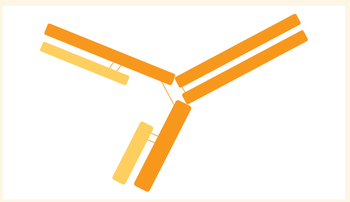
Figure 1. **CSF-1R**



ATP = adenosine triphosphate.

- 2 ligands: CSF-1, interleukin (IL)-34
- Tissue expression
  - Mononuclear phagocytic cells (monocytes)
  - Tissue macrophages
  - Kupffer cells
  - Langerhans cells
  - Microglial cells
  - Osteoclasts
  - Hematopoietic precursors
  - Trophoblasts
- Function
  - Proliferation
  - Survival
  - Differentiation
  - Chemotaxis of mononuclear phagocytic cells and their precursors
- Macrophages
  - Important roles in tissue development/homeostasis, immune responses
  - Key roles in cancer and fibrosis

Figure 2. **SNDX-6352 Antibody**



*High-affinity, humanized IgG4P contains an *S228P* mutation to stabilize the molecule and prevent Fab-arm exchange.

- High-affinity, humanized IgG4P* (KD = 4–8 pM)
- Demonstrated binding to CSF-1R variants carrying 4 different single nucleotide polymorphisms/mutations (*VG2G, A245S, P247H, V279M*)
- Blocks binding of both CSF-1 and IL-34
- Potent inhibitor of ligand-induced monocyte activation
- Cross-reacts with cynomolgus monkey CSF-1R
  - Does not cross-react with rodent CSF-1R
  - Rodent surrogate generated (Ab535)
- No evidence of antibody-mediated receptor internalization or activation

METHODS

- This study was a double-blind, randomized, placebo-controlled, single-ascending-dose, phase I trial in healthy volunteers
- The planned doses were 0.15 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 6.0 mg/kg, and 10.0 mg/kg
- Subjects received SNDX-6352 or placebo as a 30-minute intravenous infusion
- All treated subjects were observed for 72 hours post infusion and underwent follow-up evaluations for 12 weeks in the mornings of days 8, 15, 22, 29, 57, and 85
- Safety assessments included adverse event (AE) monitoring, clinical laboratory examinations, vital signs, 12-lead electrocardiogram, eye examination, and physical examination
- Blood samples were collected to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the antibody (change in CSF-1 and IL-34), as well as to evaluate changes in circulating classical and nonclassical CD16+ monocytes in blood and change in CSF-1 receptor occupancy

RESULTS

Demographics/Safety

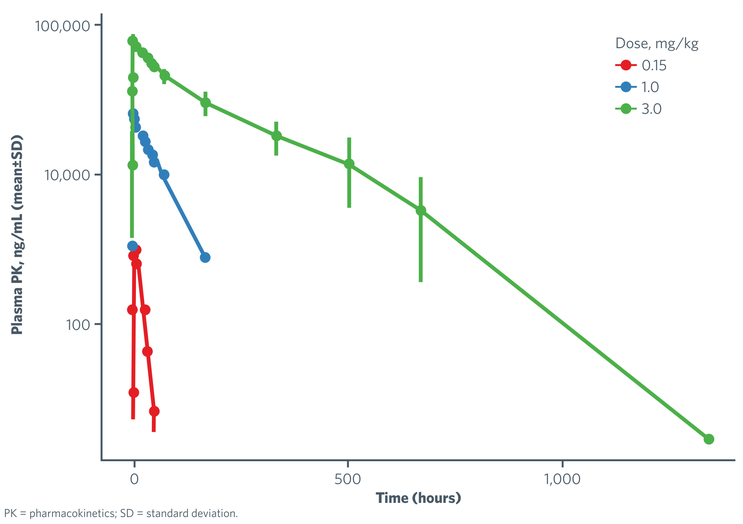
- The first 3 placebo-controlled cohorts were completed with 14 subjects receiving SNDX-6352 (2 at 0.15 mg/kg, 6 at 1.0 mg/kg, and 6 at 3.0 mg/kg) and 6 subjects receiving placebo (2 in each cohort)
- Dosing up to 1.0 mg/kg was tolerated well, with the most common complaint being mild to moderate itching (lasting 2 or 3 days)
- At the 3.0 mg/kg dose, similar itching complaints were observed. At this dose, mild to moderate eyelid edema was observed in all 6 subjects receiving SNDX-6352 (median duration of 40 days), with no impact on vision. Dose escalation was then terminated

Table 1. **Adverse Events**

		Dose Level 1		Dose Level 2		Dose Level 3	
Category	Adverse Event	0.15 mg/kg (n=2)	Placebo (n=2)	1.0 mg/kg (n=6)	Placebo (n=2)	3.0 mg/kg (n=6)	Placebo (n=2)
Eye disorders	Eyelid edema	—	—	—	—	**6**	1
	Eyelid pain	—	—	—	—	**2**	—
	Increased lacrimation	—	—	—	—	**2**	—
	Eyelid disorder	—	—	—	—	**2**	—
	Erythema of eyelid	**1**	—	—	—	**1**	—
	Eye pain	—	—	—	—	—	1
Skin and subcutaneous tissue disorders	Pruritus	—	—	**3**	—	**4**	—
	Erythema	—	—	**1**	1	**2**	—
	Oral/facial swelling	—	—	—	—	**1**	—
	Acne	—	—	—	—	**1**	—
	Urticaria	—	—	—	—	**1**	—
Nervous system disorders	Headache	**1**	2	**2**	—	**2**	—
	Paresthesia	—	—	—	—	**1**	—
	Vasovagal reaction	**1**	—	—	—	—	—
	Somnolence	—	—	—	—	**1**	—
Infections and infestations	Upper respiratory tract infection	—	1	**3**	—	**1**	—
	Stye	—	—	**1**	—	—	—
	Oral herpes	—	1	**1**	—	—	—
General disorders and administration site conditions	Injection site reaction	**1**	—	**1**	—	**2**	—
	Fatigue	—	—	—	—	**2**	—
	Feeling jittery	—	—		—	**1**	—
Musculoskeletal and connective tissue disorders	Back pain	—	—	**1**	—	—	—
	Facial pain	—	—	—	—	**1**	—
	Neck pain	—	—	—	—	**1**	—
Injury, poisoning, and procedural complications	Contusion	—	—	—	—	**1**	—
Gastrointestinal disorders	Salivary gland mucocele	—	—	—	—	**1**	—
Respiratory, thoracic, and mediastinal disorders	Oropharyngeal pain	—	1	**1**	—	—	—

Effects of SNDX-6352 on Pharmacokinetic and Pharmacodynamic Parameters

Figure 3. **Pharmacokinetic Profile of SNDX-6352**

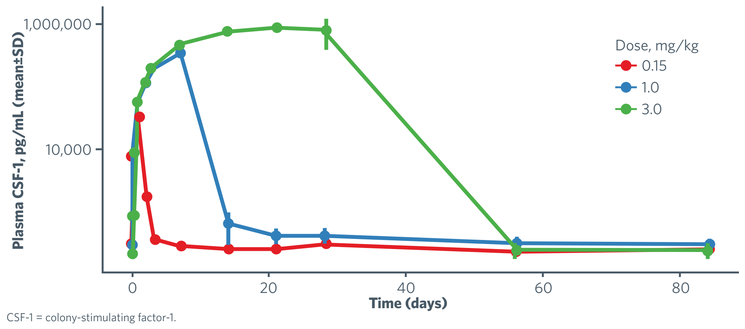


PK = pharmacokinetics; SD = standard deviation.

- Maximum concentration increases corresponded with dose, while area under the concentration-time curve increases were greater than dose proportional, indicating nonlinear PK. The observed concentration-time profiles are consistent with drugs that exhibit target-mediated drug disposition

RESULTS *Continued*

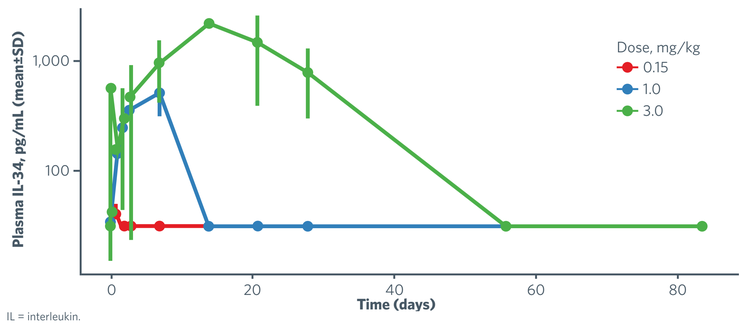
Figure 4. **Effect of SNDX-6352 on CSF-1 Levels**



CSF-1 = colony-stimulating factor-1.

- Increased CSF-1 concentrations were observed at all dose levels. Peak concentrations of 914.5 ng/mL were observed at approximately 20 days after the 3.0-mg dose

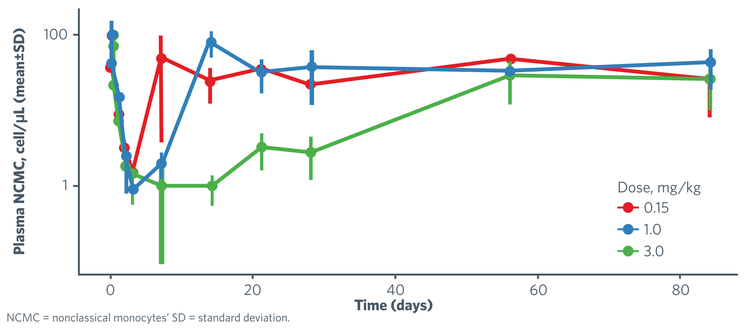
Figure 5. **Effect of SNDX-6352 on Interleukin-34 Levels**



IL = interleukin.

- Increased IL-34 was detected after the 1.0-mg and 3.0-mg dose in a pattern consistent with that seen for CSF-1

Figure 6. **SNDX-6352 Reduces Circulating Nonclassical Monocytes**



NCMC = nonclassical monocytes' SD = standard deviation.

- In blood, a transient reduction in nonclassical CD16+ monocytes was observed
- In addition, elevations in lactate dehydrogenase and aspartate aminotransferase levels were seen (data not shown)

CONCLUSIONS

- The observed increases for both CSF-1 and IL-34, along with transient suppression of circulating monocyte levels, are consistent with the mechanism of action of SNDX-6352
- The PK/PD concentration-time profiles are characteristic of drugs that exhibit target-mediated drug disposition
- Consistent with other agents in this class, eyelid swelling/periorbital edema was observed, limiting dose escalation in healthy volunteers
- These data support initiation of clinical studies in cancer patients (phase I dose-escalation trial ongoing, NCT 03238027)

References

1. Noy R, Pollard JW. *Immunity.* 2014:41;49-61; **2.** Zhu Y et al. *Cancer Res.* 2014: 74;5057-5069.

Acknowledgments

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