

**Abstract: Introduction:** Ulcerative colitis (UC) is a chronic inflammatory disease of the colonic mucosa. Infliximab has long been a standard therapy for moderate to severe UC. IV followed by oral cyclosporine (CsA) has demonstrated similar safety and efficacy to infliximab for the treatment of acute UC; however, prolonged use for the maintenance of remission is limited due to concerns about side effects of systemically available CsA. There remains a need for an oral CsA therapy that controls UC disease activity while minimizing systemic exposure. ST-0529 is a novel, orally administrated, solubilized CsA formulation designed to optimize the delivery of drug to colonic tissue while minimizing systemic absorption. **Objective:** To characterize the whole blood pharmacokinetics of ST-0529 following single and multiple oral doses (ODs), and compare to the pharmacokinetic profile following CsA IV infusion in healthy male subjects. To establish CsA colonic mucosa concentrations following single or twice-daily (BID) ODs and various dosage regimens of ST-0529 for seven days, comparing them to CsA continuous IV infusion. **Methods:** In Stage 1, a total of 24 eligible healthy male subjects received either 2 mg/kg/day of IV CsA over two consecutive 12-hour infusions (per protocol) and a once- or a twice-daily ODs of 75 mg ST-0529 for seven days. The protocol allowed to conduct further investigations with alternative ST-0529 doses and dose frequencies after review of Stage 1 data. Following this review, eight subjects recruited to Stage 2 received 37.5mg ST-0529 once-daily orally for seven days. A further eight subjects recruited to Stage 3 received 150mg ST-0529 BID ODs for seven days. **Results:** Single dose systemic exposure to CsA was considerably lower (~5%) following treatment with ST-0529 ranging from 37.5 mg to 300 mg daily for seven days compared with 24-hour continuous IV 2 mg/kg/day infusion. All ST-0529 dosage groups tested achieved colon tissue concentrations comparable to or above that attained during IV CsA administration with the 75 mg BID and 150 mg BID groups sustaining the minimum tissue concentrations achieved following IV infusion and being substantially higher than that achieved by 37.5mg OD and 75 mg OD groups. A total of 26 subjects (54.2%) reported treatment-emergent adverse events (TEAEs) during the study. All were mild or moderate; there were no severe TEAEs reported. **Conclusion:** The study demonstrated ST-0529 achieved similar or higher colonic tissue concentrations than continuous IV CsA infusion with substantially lower systemic exposure. These data suggest that ST-0529 may provide similar or enhanced efficacy to IV or oral CsA formulations with an improved tolerance profile and thus support further development as a treatment for the induction and maintenance of remission in UC.

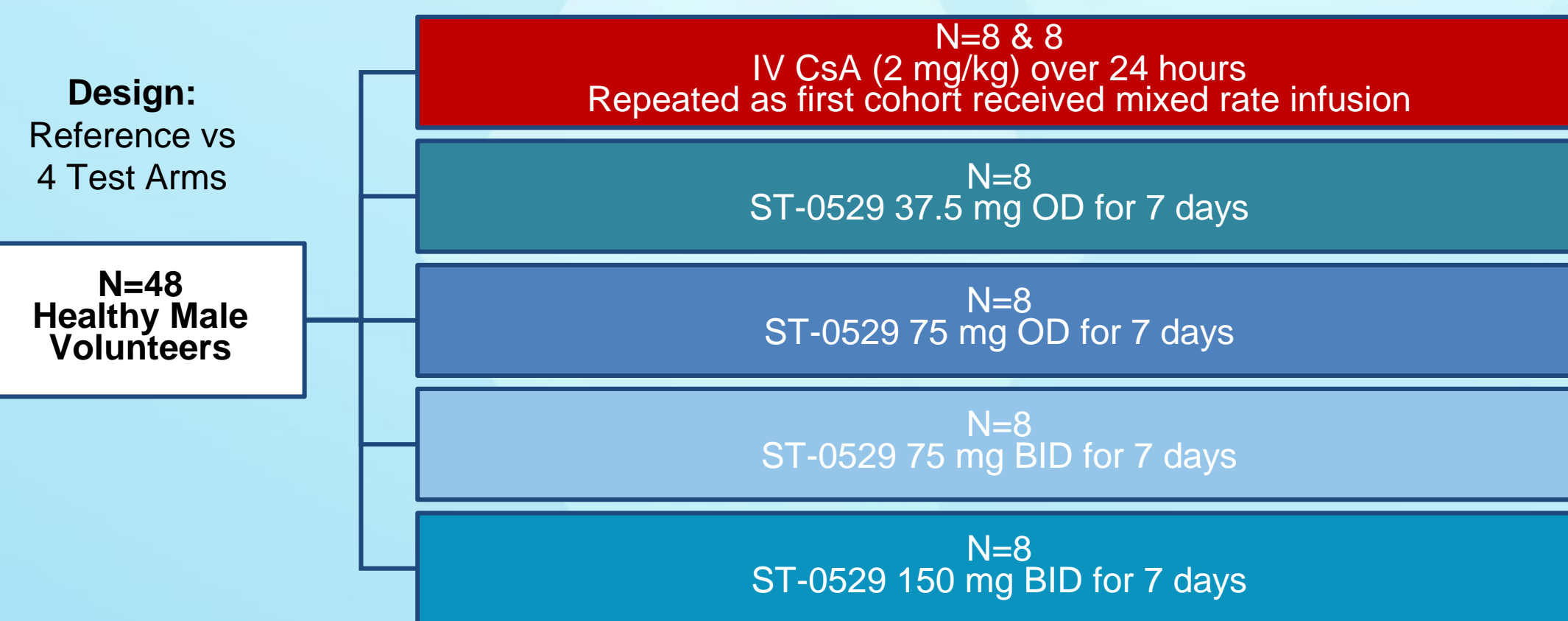
## Background

- Cyclosporine (CsA):
  - Effective for the treatment of acute UC;
  - Long-term maintenance use of CsA is limited by its side effects related to systemic absorption
- ST-0529:
  - Novel, orally administrated, solubilized CsA formulation
  - Designed to optimize the delivery of drug to colonic tissue while minimizing systemic exposure

## Objectives

- Characterize the whole blood pharmacokinetics (PK) of ST-0529 following single and multiple oral doses (ODs)
- Compare to the pharmacokinetic profile following CsA IV infusion in healthy male subjects
- Establish CsA colonic mucosa concentrations following single or twice-daily (BID) ODs and various dosage regimens of ST-0529 for seven days, comparing them to CsA continuous IV infusion

## Methods

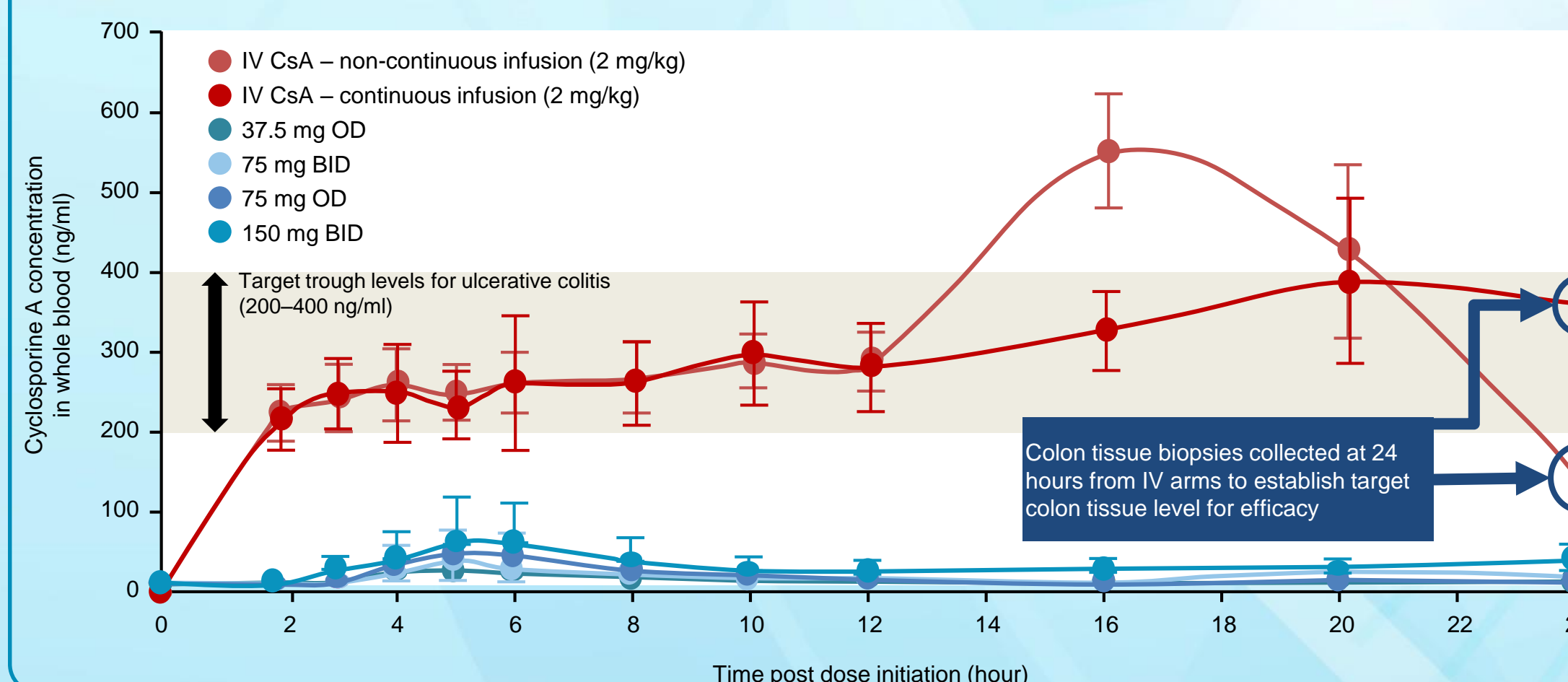


## Results

**TABLE 1: Mean CsA concentrations and AEs**

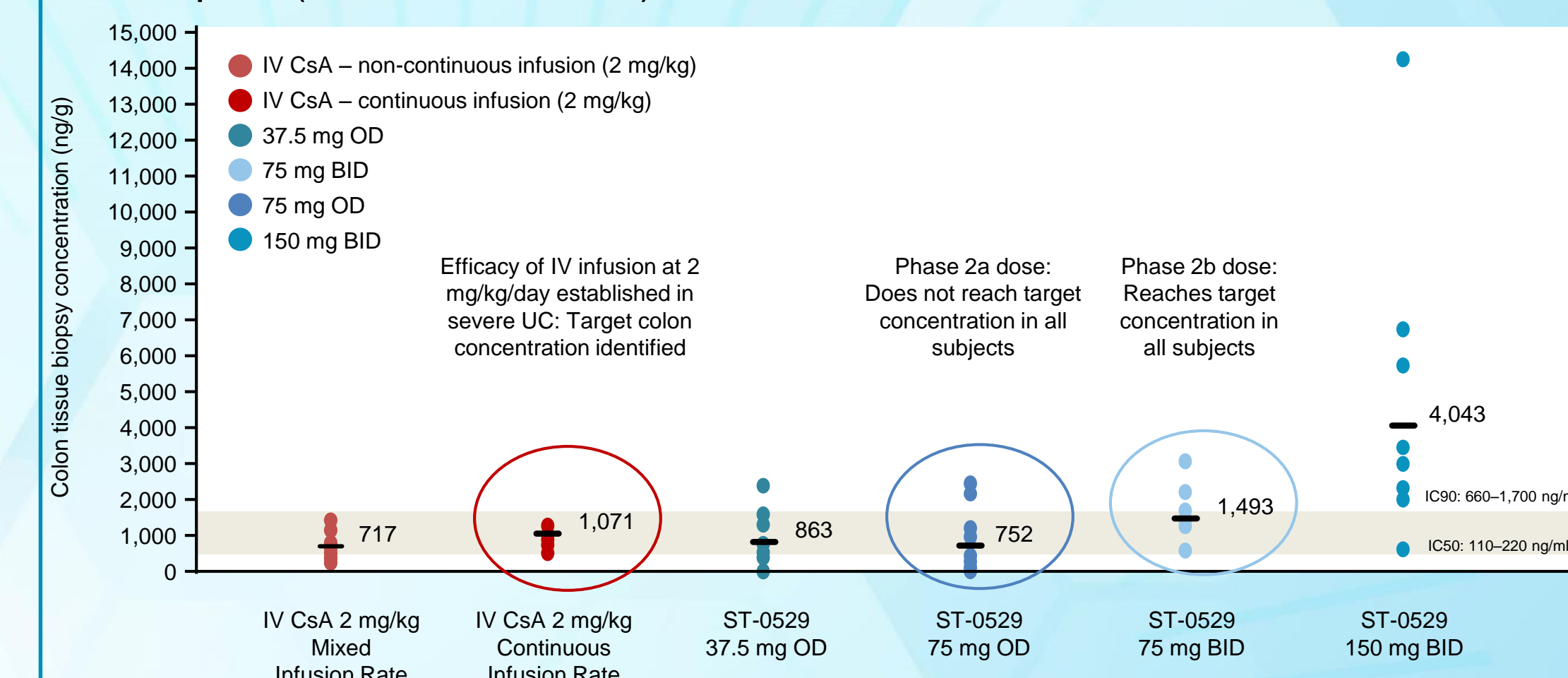
	IV CsA Group 1 (two consecutive MIXED RATES 12-hour infusions) N=8	IV CsA Group 2 (two consecutive FIXED RATES 12-hour infusions) N=8	ST-0529 37.5 mg once daily N=8	ST-0529 75 mg once daily N=8	ST-0529 75 mg twice daily N=8	ST-0529 150 mg twice daily N=8
Single dose plasma concentration AUC <sub>inf</sub> (ng.h/mL) – geometric mean (CV%)	8769.5 (13.4)	8274.5 (19.2)	117.9 (53.3)	218.3 (61.8)	265.9 (63.1)	700.4 (56.1)
Colonic tissue concentration (ng/g) – geometric mean (CV%)	717 (49.5)	1071 (25.1)	863 (68.2)	752 (80.6)	1493 (31.8)	4043 (84.8)
Subjects with TEAEs [n (%)]	5 (62.5)	3 (37.5)	6 (75.0)	3 (37.5)	3 (37.5)	6 (75.0)

**FIGURE 1: Blood PK Results**



## Results

**FIGURE 2: Cyclosporine A Concentration (ng/g) in Colon Tissue Samples (Geometric Mean)**



## Conclusions

- ST-0529 achieved similar or higher colonic tissue concentrations than continuous IV CsA infusion with substantially lower systemic exposure
- These data suggest that ST-0529 may provide similar or enhanced efficacy to IV or oral CsA formulations with an improved tolerance profile and thus support further development as a treatment for the induction and maintenance of remission in UC