

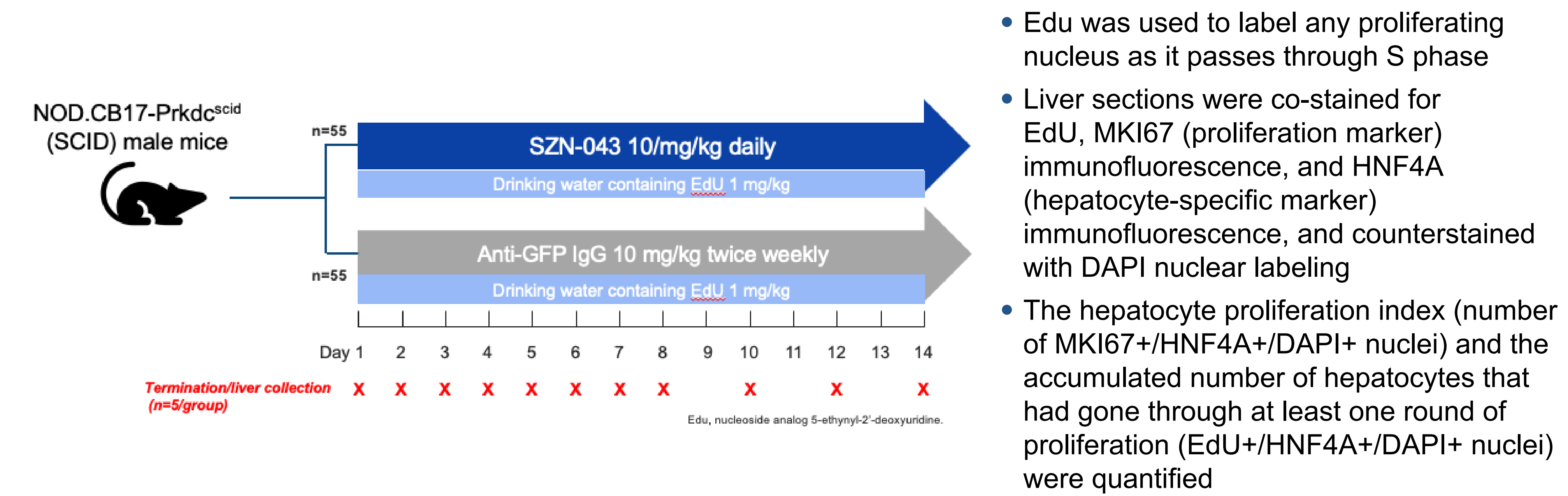
SZN-043 Induced Quick and Robust Hepatocyte Proliferation in a 14-Day Daily Dosing Edu-labeling Study in SCID Mice

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Background

- Wnt/ β -catenin signaling plays a key role in hepatocyte regeneration in homeostasis and after liver injury
- R-spondins (RSPO) amplify the signal of Wnt ligands by stabilizing and increasing the amount of Wnt receptors on the cell surface
- We previously showed that our hepatocyte-targeted RSPO mimetic, SZN-043, specifically induced Wnt target gene expression in the liver and promoted hepatocyte proliferation in mice
- This study aimed to evaluate the kinetics and the overall effects of SZN-043-induced hepatocyte proliferation in a 2-week daily SZN-043 dosing schedule

Methods



Results

Figure 1. Significant Proliferation of Hepatocytes in Response to SZN-043 Was Quick and Transient

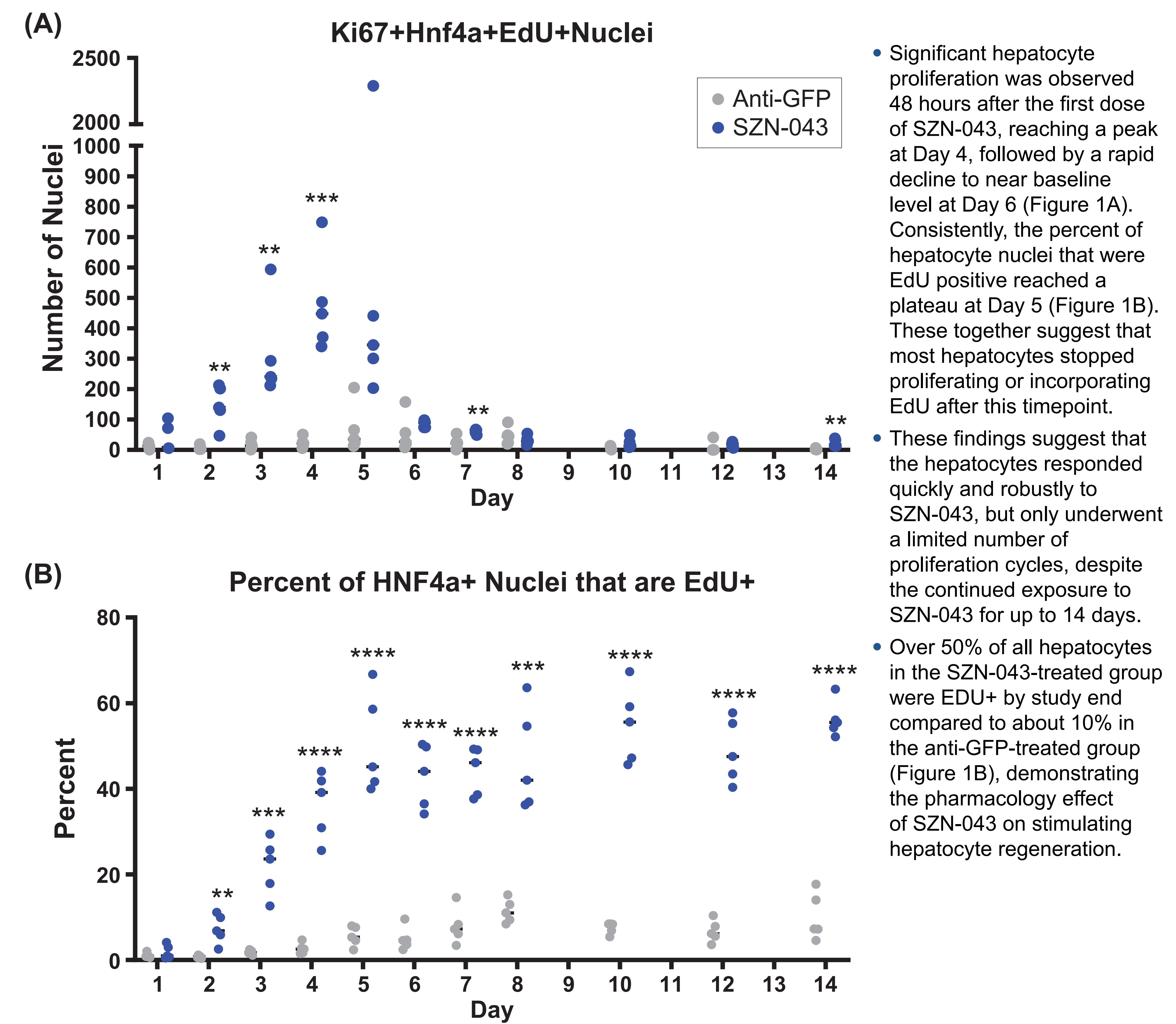


Figure 2. Liver mRNA Expression of Axin2 was Significantly Increased with SZN-043

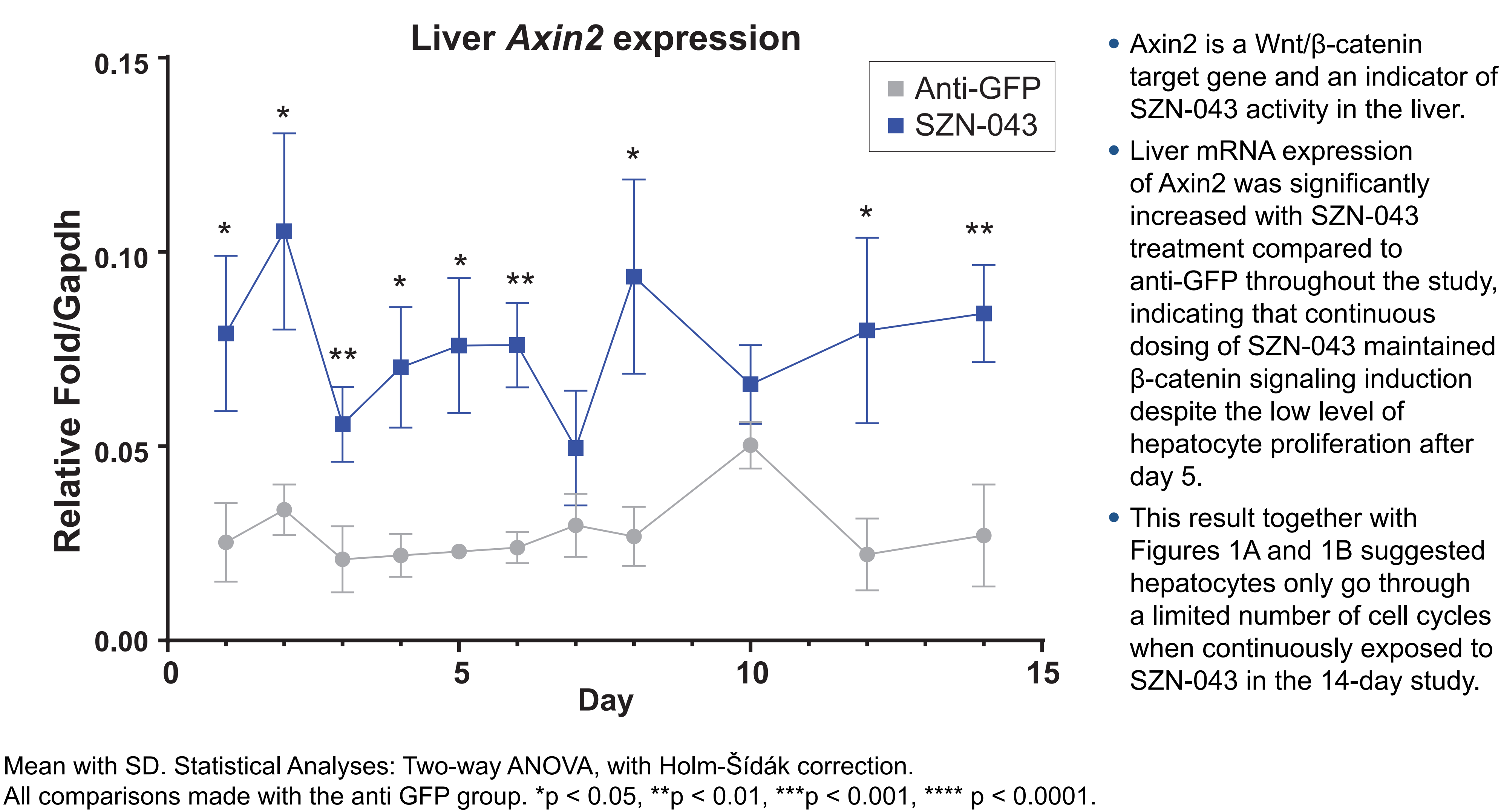
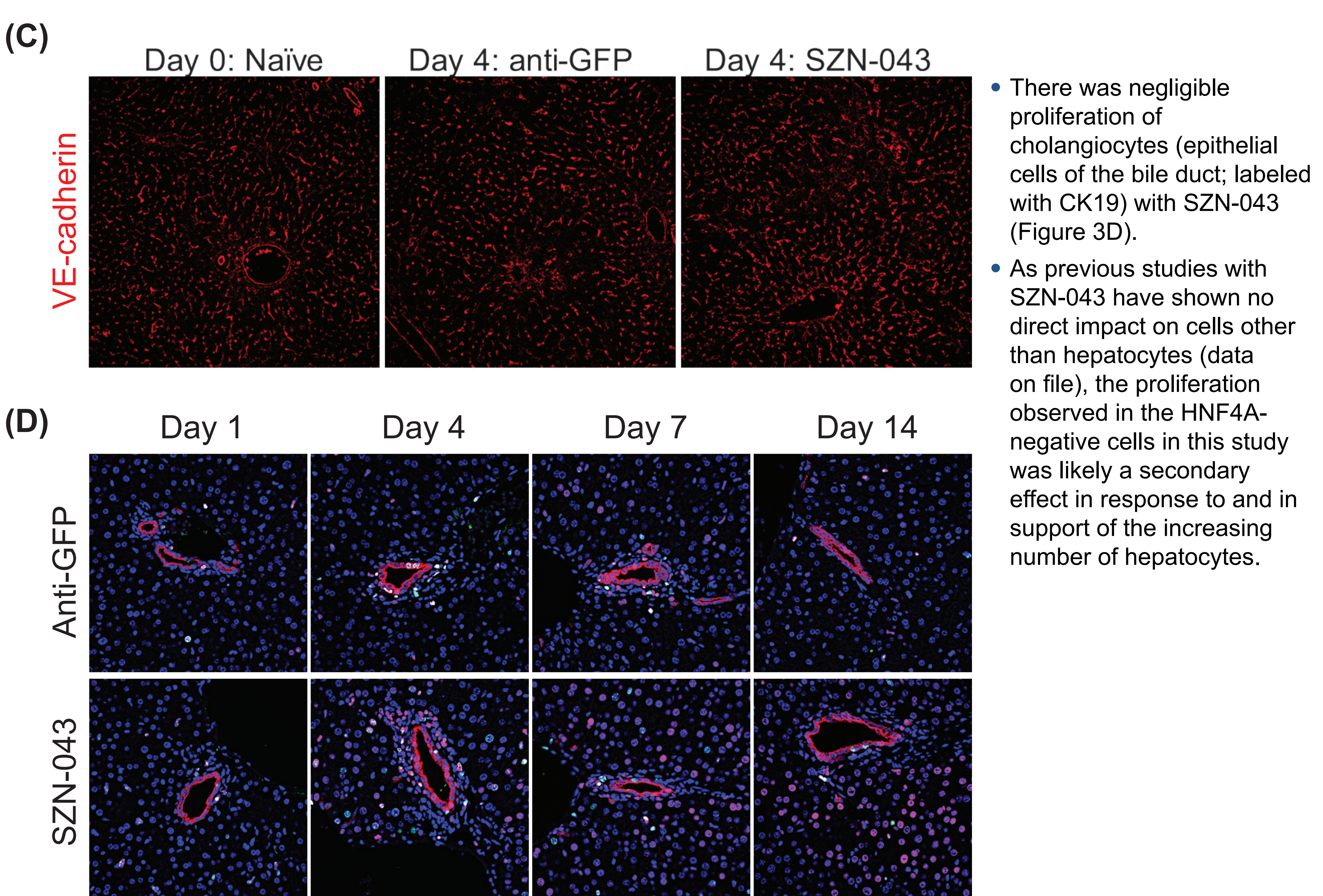
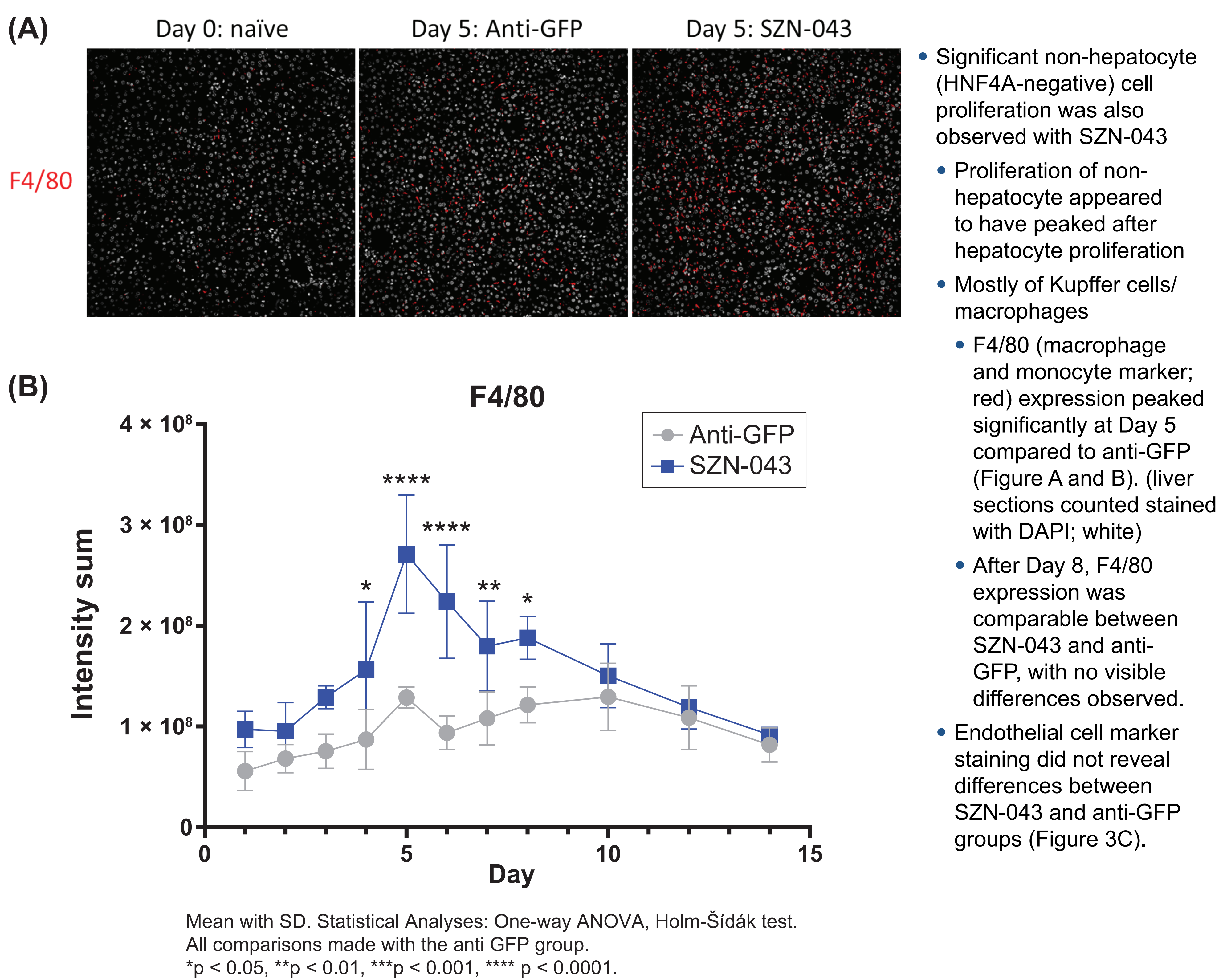


Figure 3. Non-Hepatocyte (HNF4A-negative) Cell Proliferation was Significant with SZN-043



Conclusions

- SZN-043 induced a rapid transient increase in hepatocyte proliferation, followed by rapid a decline to baseline despite continued exposure to SZN-043 and β -catenin signaling induction for up to 14 days.
- Hepatocyte proliferation induced by SZN-043 was self-limited and likely controlled by other mechanisms controlling cell proliferation (Sarkar A. et al., 2021).
- Proliferation observed in the HNF4A-negative cells was likely due to the tissue responding to the large number of proliferating hepatocytes.

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