The intestinal absorption of cholesterol is mediated by a multi-pass membrane protein, Neimann-Pick C1-Like 1 (NPC1L1), the molecular target of a cholesterol lowering therapy, ezetimibe. While ezetimibe gained FDA approval in 2002, its mechanism of action has remained unclear. Here we present two cryo-EM structures of NPC1L1, one in its apo-form and the other complexed with ezetimibe. The apo-form represents an open state in which the N-terminal domain (NTD) packs loosely to the rest of NPC1L1, allowing the NTD central cavity accessible for cholesterol loading. The ezetimibe-bound form signifies a closed state in which the NTD rotates ~60 degrees, creating a continuous tunnel enabling cholesterol movement into the plasma membrane. Remarkably, ezetimibe blocks cholesterol transport by occluding the tunnel instead of competing with cholesterol binding. These findings provide insights into the molecular mechanisms of NPC1L1 mediated cholesterol transport and ezetimibe inhibition.