



## **1                    DNL104 LAY SUMMARY**

DNL104 is a new compound that was developed to inhibit a protein called RIPK1. Many types of cells in the body have RIPK1, including cells in the brain. Inhibition of RIPK1 reduces inflammation and cell death and this may be beneficial in neurologic diseases like Alzheimer's or amyotrophic lateral sclerosis (ALS).

In this Phase 1 study, DNL104 in the form of capsules was given to healthy volunteers to assess its safety and how the body absorbs and eliminates this compound. In the first part of the study, volunteers received single doses of DNL104. The first 6 subjects received 5 mg, and in the subsequent groups the dose of DNL104 was gradually increased (15, 50, 100, 150, 225 mg) to determine how well tolerated it was. Some subjects in each group received placebo (a capsule with no actual DNL104) to determine whether the side-effects the volunteers experienced were due to DNL104 or not. Single doses of DNL104 up to 225 mg were very well tolerated and there were no side-effects or changes in blood laboratory tests, heart rhythm, blood pressure, or brain function that appeared to be due to DNL104.

Measurements of the amount of DNL104 in blood showed that it was quickly eliminated from the body. This meant that it would be necessary to give DNL104 3 times per day to inhibit RIPK1 enough. Measurements of the amount of DNL104 in cerebrospinal fluid showed that it was able to diffuse from the blood into the brain, which is necessary for the potential benefit in neurologic diseases. The effect of DNL104 on RIPK1 was confirmed in an assay in blood cells.

After completing the single-dose part of the study, new groups of volunteers received 3 doses (morning, midday, and evening) of DNL104 for 10 days to assess the safety and tolerability of repeated dosing. The first group received 50 mg three times a day for 10 days, then the next group received 100 mg three times a day for 10 days. Repeated doses of DNL104 were also very well tolerated during the 10 days of dosing; however, after the end of dosing, 3 subjects had changes in blood tests that indicated mild damage to the liver. These changes were reversible (they went away after a few weeks of follow-up); however, it was decided to stop the development of this compound because of potential risk for more severe liver damage when DNL104 is given for longer periods of time.