

# Intravenous Sampling and Administration Using Instech Vascular Access Buttons<sup>™</sup> in Rodents: **Pathology Findings Related to Indwelling Vascular Catheter**

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# ABSTRACT

Repeated reliable access to the vascular space in rodents can be challenging in preclinical modeling. While vascular access catheterization has been extensively used in the past, Vascular Access Buttons (VAB<sup>™</sup>, Figure 1) are quickly becoming a more common method of external access for rodents. This approach minimizes potential trauma to the tail vein, increases the success rate of repeated intravenous administrations, and allows for continuous and intermittent infusion designs. While Vascular Access Buttons (VAB<sup>™</sup>) have become a more conventional method for vascular access catheterization, there have been some histopathological observations related to the indwelling vascular catheter and at the exteriorization site of the VAB<sup>™</sup> that might be a confounding factor in the histopathological and hematological evaluations in the study. Major pathological changes related to VAB<sup>™</sup> included mild to moderate ulceration and/or necrosis of the skin and mild chronic granulomatous inflammation (including thread-like foreign bodies) at the VAB<sup>™</sup> surgical site (skin Figures 2 and 3); and moderate thrombus formation, minimal perivascular hemorrhage, and fibroplasia at the catheter-implanted administration site (vena cava, Figures 4 and 5). Additionally, inflammatory changes along with thrombus in the lungs and the perivascular/sinusoids of the liver were likely associated with administration site changes (thromboembolism, Figures 6 and 7). Even though there were histopathological challenges associated with the use of VAB<sup>™</sup>s, findings were adequately documented and assessed to be associated with the administration method. In addition, the overall number of affected animals was limited and did not adversely impact study outcomes, demonstrating that this administration method is suitable for preclinical safety assessments.

# BACKGROUND

Vascular Access Buttons (VAB<sup>™</sup>) offer a permanent transcutaneous catheter solution for blood collection and dose administration in a closed system. In chronic toxicological studies, long-term catheter patency is crucial to maintain access to the vasculature and allow for repeated sampling and dosing. Using a closed system, like VAB<sup>™</sup>, allows for social group housing, an important animal welfare factor, while also contributing to stress reduction by promoting more freedom of movement due to shortened and less restrictive restrain compared with traditional rodent restrainers. This retrospective review of multiple studies, conducted at our Testing Facility in Everett, Washington, summarizes histopathological observations related to the indwelling vascular catheter and at the exteriorization site of the VAB<sup>™</sup> that might be a confounding factor in the histopathological and hematological evaluations in the study.

## METHODS

Naïve male and female Sprague Dawley rats 9 to 10 weeks old at initiation of dosing. Animals were pre-implanted with femoral catheters and single-channel vascular access buttons. Animals were used as vehicle control in two studies conducted at Altasciences. Vehicles were: 20 mM Histidine, 240 mM Sucrose pH 6 or Sodium Chloride 0.33 wt%, PS-80 0.01 wt%, Sodium Acetate 100 mM pH 6.5. The vehicle control was administered by intravenous bolus injection via VAB<sup>™</sup> once weekly for 5 weeks. The catheter was flushed using 0.1 mL of 0.9% Saline post completion of each dose administration. Animals were necropsied at either end of dosing or following an 8-week recovery period.



Figure 1. Vascular Access Button<sup>™</sup> location



Figure 2. Granulomatous inflammation (with surgical threads) of the skin at VAB site (catheterimplanted surgical site in the skin)



Figure 3. Granulomatous inflammation (with bacterial colonies) of the skin at VAB site (catheterimplanted surgical site in the skin)



Figure 4. Thrombus formation (fibrinous/cellular) at the catheter-implanted administration site (vena cava)



**Figure 5.** Thrombus formation (fibrinous/cellular with mineralization) at the catheter-implanted administration site (vena cava)



Figure 6. Thrombus formation (organizing) at the catheter-implanted administration site (vena



Histopathological changes related to VAB<sup>™</sup> included mild to moderate ulceration and/or necrosis of the skin at the VAB<sup>™</sup> surgical site with mild chronic granulomatous inflammation that included thread-like foreign bodies possibly related to the composition of the VAB<sup>™</sup> and bacterial infection due to surgical implantation (Figures 2 and 3). At the catheter-implanted site (vena cava), moderate fibrinous and cellular thrombus formation, sometimes associated with mineralization and minimal perivascular hemorrhage and fibroplasia, was observed (Figures 4 and 5). The thrombus showed an organization trend during administration but was not observed to block blood flow (Figure 6). Additionally, inflammatory changes along with thrombus in the lungs and in the perivascular/sinusoids of the liver were noted and likely associated with thromboembolism, similar to conventional catheter-based administration. (Figure

Even though there were histopathological challenges associated with the use of VAB<sup>™</sup>s, findings were adequately documented and assessed to be associated with the administration method. In addition, the overall number of affected animals was limited and did not adversely impact study outcomes, therefore demonstrating that this method of administration is suitable for preclinical safety assessments.



Figure 7. Perivascular inflammatory cell infiltrates in the liver

# DISCUSSION

### CONCLUSION