Long Acting Injectable FHD-609 Micro-suspension: A Potent BRD9 Degrader with Comparable Efficacy, Reduced Frequency of Dosing in Preclinical Models

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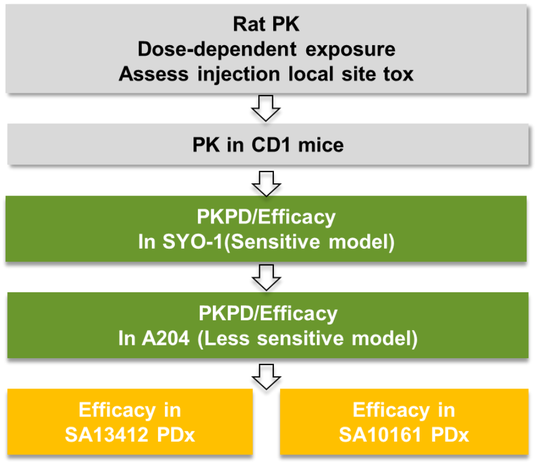
Abstract

FHD-609, a potent heterobifunctional degrader of BRD9, has been administered intravenously (i.v) in medical facilities twice weekly during clinical trials. In order to facilitate less frequent and more convenient patient-centric dosing, a long acting injectable (LAI) formulation was developed that allows subcutaneous (s.c) dosing every 4 weeks. The formulation is an aqueous micro-suspension containing the drug along with a polymer and surfactant which provides sustained release of FHD-609 upon injection. We compared the LAI formulation dosed once every 4 weeks to the i.v formulation dosed twice a week for the pharmacokinetic (PK) and pharmacodynamic (PD) properties, as well as the efficacy of the LAI in xenograft models of different sensitivities, including cell line-derived xenografts (CDX) and patient-derived xenografts (PDX). Our results showed that a single dose of the LAI formulation was well-tolerated in mice and exhibited a sustained and stable PK profile for up to 28 days. Moreover, it demonstrated comparable *in vivo* efficacy and BRD9 protein degradation to the standard i.v administration. The LAI FHD-609 formulation has the potential to offer better patient compliance and acceptance in clinical settings than i.v dosing. The LAI formulation provides a promising and effective drug delivery option for various protein degraders that are not orally bioavailable.

In-vivo assessment of LAI FHD-609



Single dose of FHD-609 LAI micro-suspension maintained plasma PK and BRD9 degradation levels up to 28 days

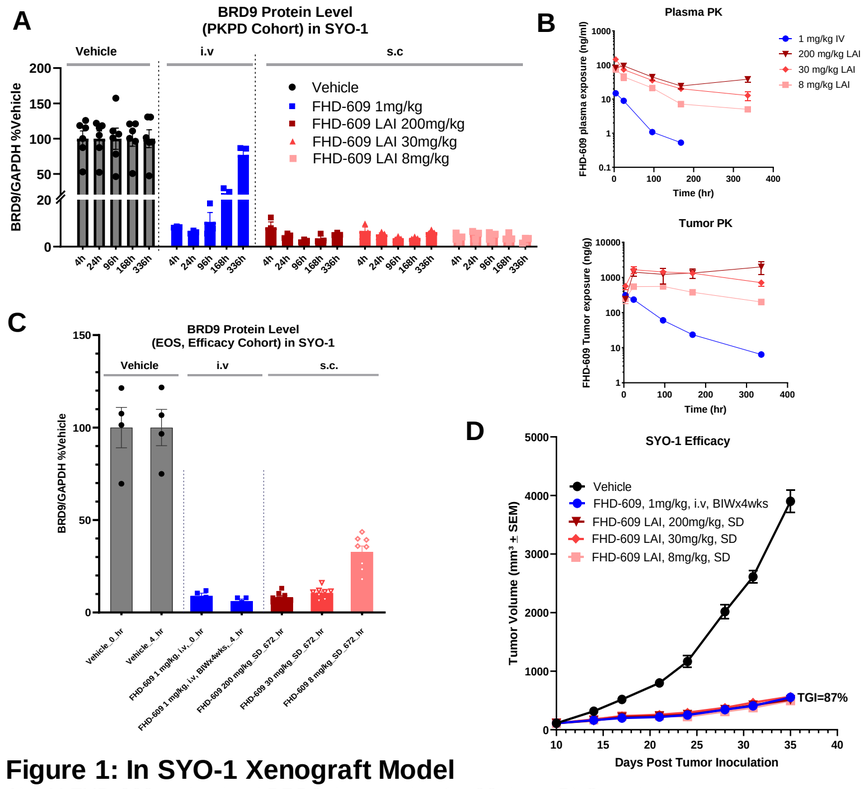


Figure 1: In SYO-1 Xenograft Model
A) LAI FHD-609 maintained BRD9 degradation for 28 days. B) Sustainable exposure achieved with LAI FHD-609. C) Dose-dependent BRD9 degradation observed at efficacy end. D) LAI FHD-609 achieved comparable efficacy.

Single dose of FHD-609 LAI micro-suspension achieved dose-dependent *in vivo* anti-tumor activities

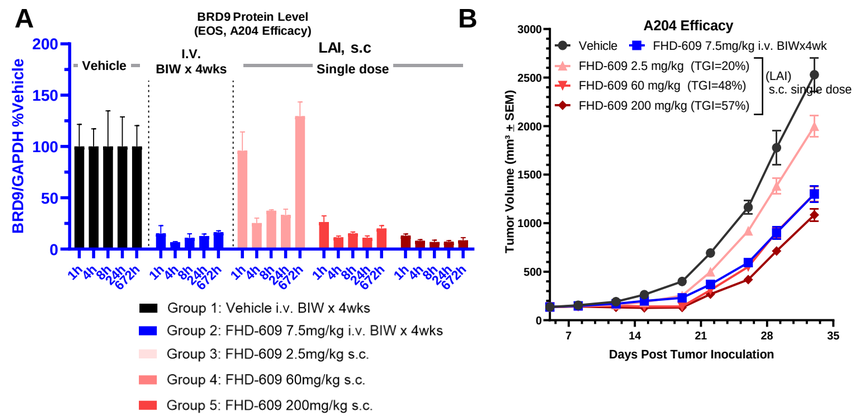


Figure 2: In A204, Rhabdomyosarcoma Xenograft Model
A) Robust, dose-dependent BRD9 protein degradation observed with FHD-609 i.v. and LAI formulations at efficacy end; B) Dose-dependent in vivo anti-tumor activity.

PDX Models showed sensitive to BRD9 degradation

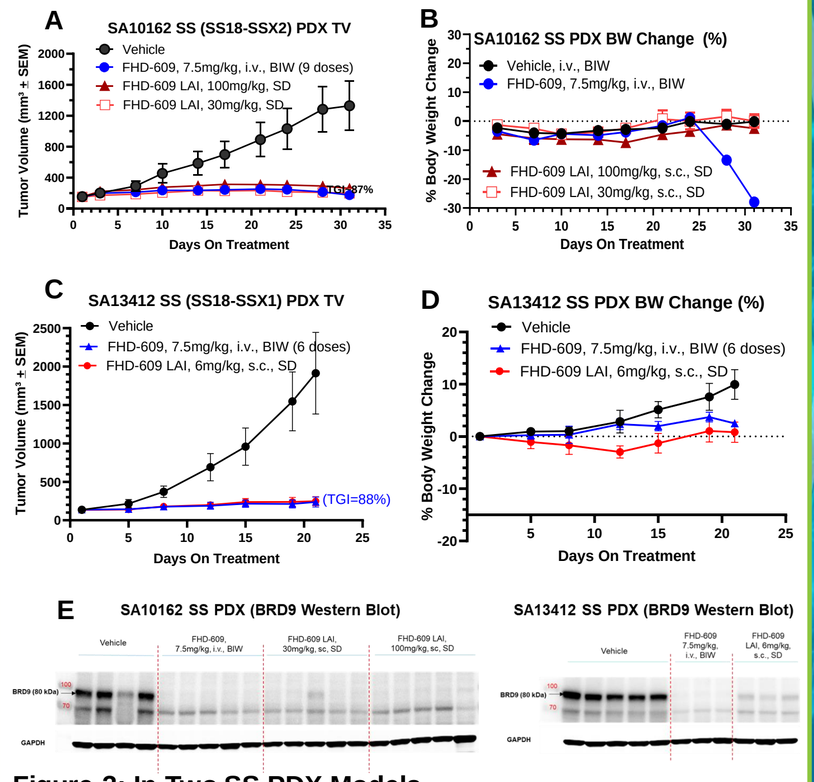


Figure 3: In Two SS PDX Models
A) FHD-609 IV and LAI formulations equally effective in SA10162 and SA13412 PDX models. LAI achieved comparable efficacy with 1/9th of total IV dosage in SA13412. B) IV administration twice weekly caused more weight loss than LAI formulation. C) Both formulations well tolerated in SA13412 model. D) Robust degradation of BRD9 protein observed with FHD-609 IV and LAI formulations in both PDX models.

Conclusions

I. Single dose of LAI FHD-609 micro-suspension demonstrated sustained plasma PK, resulted in potent BRD9 target degradation, and significantly inhibited tumor growth in both CDX and PDX models.

II. LAI FHD-609 micro-suspension is as effective as the i.v formulation, making it versatile and safer with less frequent dosing.

III. The LAI formulation emerges as a promising and efficient drug delivery solution for protein degraders lacking oral bioavailability.