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A clinical update on BLU-782, an investigational ALK2 inhibitor in development for fibrodysplasia ossificans progressiva (FOP)

Alison Davis, Faris Albayya, Riadh Lobbardi, Michael Palmer, Cori Ann Sherwin, Sara Green, Faith Stevison, Sean Kim, Gordon Wilkie, Mark Hurtt[1], Robert Schwabb[2], Rachel Stewart[3], Morgan Lyon[3], Rachel Pauplis[3], Vivek Kadambi, Marion Dorsch, Andy Boral, Timothy LaBranche

Blueprint Medicines, Cambridge, MA

[1]Hurtt Consulting, San Diego, CA, [2]Celerion, Lincoln, NE, [3]InviCRO, Boston, MA

Background

Abstract

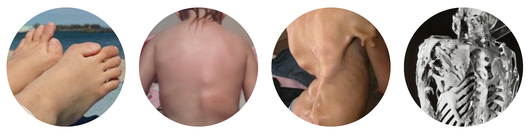
FOP is a rare, severely disabling and ultimately life-shortening disease characterized by progressive replacement of skeletal muscle and connective tissue by heterotopic bone. FOP is caused by gain-of-function mutations in ACVR1, which encodes activin receptor-like kinase 2 (ALK2). The most common ALK2 mutation identified in FOP is R206H, but other ALK2 activating mutations exist in FOP, and all impart hypersensitivity to bone morphogenetic protein ligands and a neomorphic response to activins.

BLU-782 is a potent and selective ALK2 inhibitor that has been shown to prevent injury-induced heterotopic ossification (HO) in an ALK2^{R206H} transgenic mouse model of FOP. Here, we describe preclinical data supporting the development of a prophylactic, once-daily (QD) dosing scheme for BLU-782 in FOP patients, including those with other activating ALK2 mutations.

To identify the optimal BLU-782 dosing scheme in FOP, we further evaluated the ALK2^{R206H} transgenic mouse model. FOP manifests in this model with a progression from acute muscle degeneration on the day of the injury to a fibroproliferative response by day 4 post-injury, chondrocyte proliferation and cartilage deposition by day 7, a mix of cartilage and bone by day 10 and, lastly, mature bone formation by day 14. By delaying the initiation of BLU-782 dosing for increasing times post-injury, we found that ALK2 inhibition is necessary as early as day 2 post-injury and needs to be maintained up to 12 days post-injury to fully prevent HO formation in this in vivo mouse model. This observation suggests that ALK2^{R206H} is activated shortly after muscle injury, before any detectable signs of a flare, and its activity persists until HO formation matures. Therefore, we recommend the dosing scheme for BLU-782 in the clinic to be once-daily and chronic, such that target coverage (i.e. >IC70 at Cmin) is maintained.

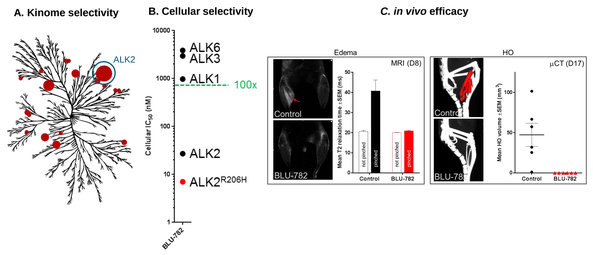
Results of the ongoing Phase 1 safety, tolerability, pharmacokinetics, and food effect trial in healthy adults will be discussed. One of the objectives of this randomized, double-blind, placebo-controlled, single and multiple ascending dose and food effect study is the recommendation of a Phase 2 dose. Blueprint Medicines plans to initiate a single-arm, open-label Phase 2 clinical trial in the fourth quarter of 2019 to evaluate the safety and tolerability of BLU-782 when administered chronically to FOP patients.

FOP is a rare genetic disease characterized by the conversion of soft tissue into bone[1]



- ALK2 missense mutations are found in 100% of FOP patients[2, 3]
  - >95% possess ALK2^{R206H}
- ALK2^{R206H} mice recapitulate all the key features of FOP[4]

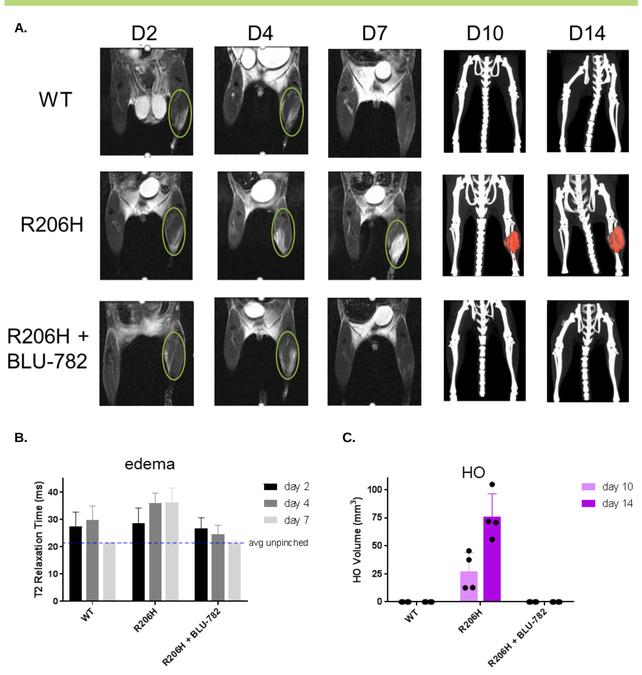
BLU-782 is a potent, selective ALK2 inhibitor that prevents edema and heterotopic bone formation in a FOP mouse model



A. BLU-782 is kinome sparing. Biochemical binding data for BLU-782 screened at 3 µM against >400 human kinases are depicted as red circles on the kinome phylogenetic tree. The size of the circle is proportional to the level of binding to each kinase. Type I TGFβ/BMP receptors including ALK2 are shown in the blue circle. **B.** BLU-782 is selective for ALK2^{R206H} over other BMP Type I ALK family receptors. Cellular IC_{50} values of BLU-782 were determined for ALK2^{R206H} and other ALK family members using SMAD1-P as a readout of activity. **C**. Prophylactic treatment with BLU-782 inhibited both injury-induced edema and HO formation in ALK2^{R206H} mice. Left panel: representative MR images of an untreated control mouse (top, arrow pointing to hyperintense region) and a BLU-782 treated mouse (bottom). Quantification of edema in both the injured leg (pinched) and contralateral leg (not pinched), measured by T2-weighted MRI on day 8 post-injury of all 6 mice/group shown in graph. Right panel: representative µCT images of an untreated control mouse (top, HO pseudo-colored in red) and a BLU-782 treated mouse (bottom). Quantification of the HO volume measured by µCT on day 17 post-injury of all 6 mice/group shown in graph.

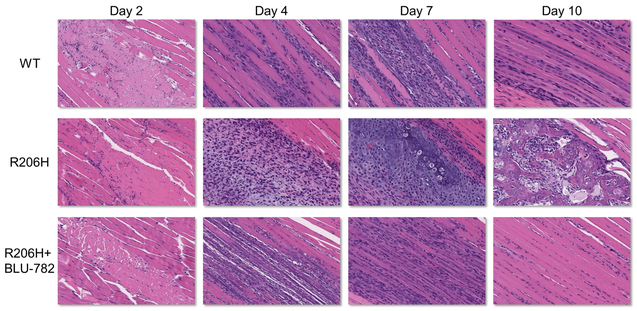
Results and discussion

BLU-782 dampens edema early and prevents HO in ALK2^{R206H} mice



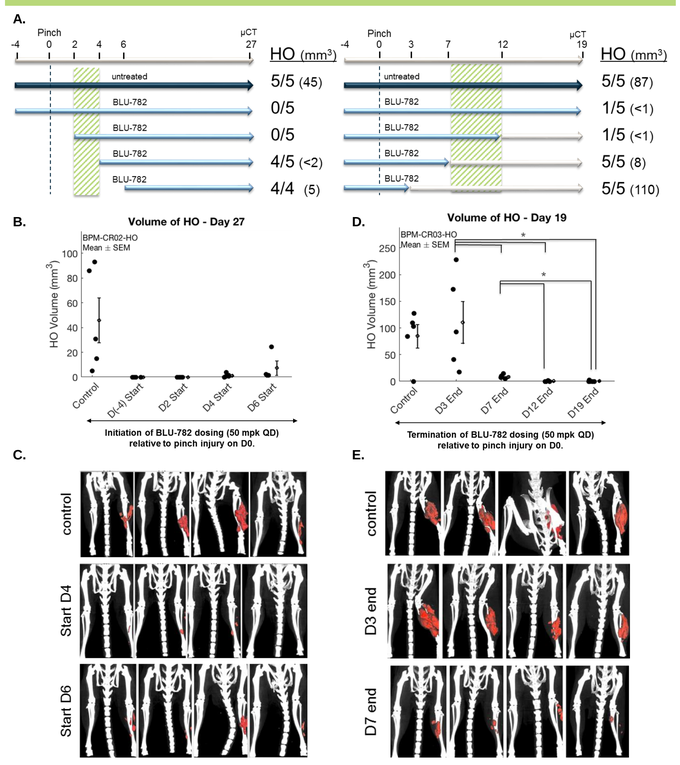
BLU-782 dampens edema early and prevents HO in ALK2^{R206H} mice. **A**. WT or ALK2^{R206H} mice were untreated or dosed prophylactically with BLU-782 before receiving a pinch injury to one leg. Animals were imaged by MR at 2, 4 and 7 days post pinch; edema in pinched legs is outlined in green circles. Animals were imaged by µCT at days 10 and 14 post pinch; HO is pseudo-colored in red. MR and µCT data from one representative animal is shown from each group. **B**. Quantification of edema in pinched legs of all animals (4 per group) as measured by MR. Average T2 relaxation time signal (ms) in all unpinched legs is shown as a baseline (blue dashed line). **C**. Quantification of HO volume in mm^3 in pinched legs of all animals (4 per group) as measured by µCT. No HO was detected in WT or R206H + BLU-782 groups.

BLU-782 enables damaged muscle to undergo a normal reparative process in ALK2^{R206H} mice.



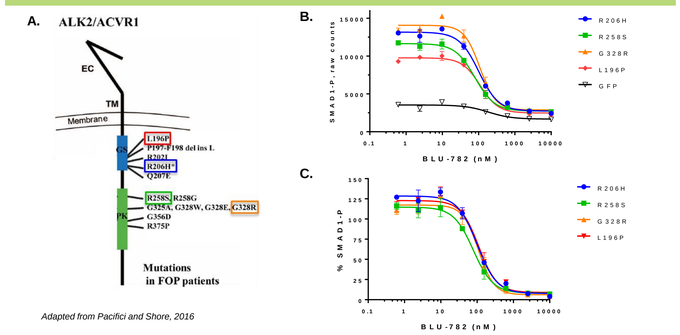
Representative photomicrographs illustrating that BLU-782 treatment allows for a normal tissue repair response after pinch injury in ALK2^{R206H} mice. WT or ALK2^{R206H} mice were untreated or dosed prophylactically with BLU-782 before receiving a pinch injury to one leg. Animals were sacrificed 2, 4, 7, or 10 days post-pinch. Pinched legs were harvested and processed for Haemotoxylin and Eosin (H&E) staining.

ALK2 inhibition by BLU-782 is required throughout the HO process to prevent bone formation



Dosing BLU-782 prophylactically is most effective for preventing HO. **A**. Study design for two studies testing efficacy of BLU-782 when dosed at various times after pinch injury (left) or when dosing was stopped early (right). The average HO volume in mm^3 in each group is listed. **B**. HO volumes of individual ALK2^{R206H} animals untreated or dosed with BLU-782 starting on Day -4, Day 2, Day 4 or Day 6 after pinch injury. **C**. µCT images of ALK2^{R206H} animals in groups that developed HO (red) from B. **D**. HO volumes of individual ALK2^{R206H} animals untreated or dosed prophylactically with BLU-782 with dosing continued until Day 3, Day 7, Day 12 or Day 19 after pinch injury. **E**. µCT images of ALK2^{R206H} animals in groups that developed HO (red) from D.

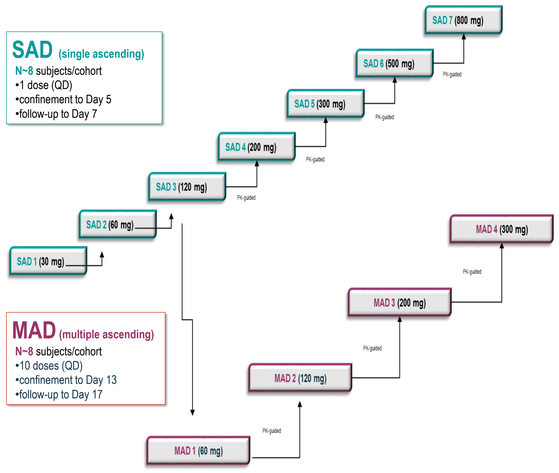
BLU-782 potently inhibits Activin A-stimulated ALK2 irrespective of the activating FOP mutation



Adapted from Pacifici and Shore, 2016

BLU-782 inhibits Activin A-stimulated ALK2 signaling in multiple FOP-mutants. **A**. Schematic representation of ALK2 denoting the location and amino acid changes of known mutations in FOP. Mutations tested in B and C are found in the glycine-serine rich domain (GS) or the protein kinase domain (PK) and are highlighted in colored boxes. **B** and **C**. HEK-293T cells expressing the ALK2^{R206H}, ALK2^{R258S}, ALK2^{G328R} or ALK2^{L196P} FOP mutations were dosed with BLU-782 and then challenged with the ligand Activin A. ALK2 activity was measured by SMAD1-P in cell lysates using a SMAD1-P AlphaLISA kit. Dose response curves are graphed as total SMAD1-P counts (B) showing the levels of SMAD1 activation observed with the different ALK2 mutations, and (C) as normalized % SMAD1-P highlighting the nearly identical IC_{50} values of BLU-782 for each ALK2 mutant.

Ph1 SAD/MAD Trial in Normal Healthy Volunteers



Study design for Phase 1 clinical trial to monitor the safety, tolerability, pharmacokinetics, and food effect of BLU-782 in Healthy Adults (NCT03858075).

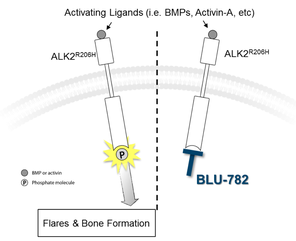
BLU-782

- well-tolerated at all dose levels
- increased exposure with increasing dose
- half-life is approximately 24 hours
- PK and PD results support once-daily dosing regimen
- Phase 2 dose identified as 200 mg, once-daily

BLU-782: an ALK2 inhibitor specifically tailored for FOP

BLU-782 is highly selective

BLU-782 targets the root cause of FOP



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5. Pacifici, M and E. M. Shore. Common mutations in ALK2/ACVR1, a multi-faceted receptor, have roles in distinct pediatric musculoskeletal and neural orphan disorders. Cytokine & Growth Factor Reviews. 27, 93–104 (2016).