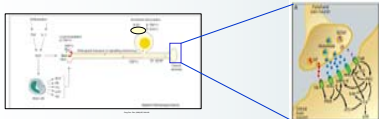


Introduction

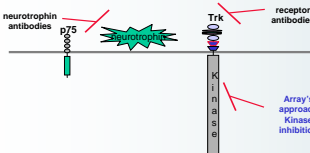
- ARRY-470 is a small molecule inhibitor of the Trk receptor signaling pathway targeting TrkA, TrkB and TrkC
- ARRY-470 has demonstrated significant, and often superior, efficacy to standard pain relievers in a variety of animals models of pain including:
 - Rat Complete Freund's Adjuvant (CFA) in the hind paw
 - Rat Collagen-Induced Arthritis
 - Rat osteoarthritis induced by intraarticular injection of CFA
 - Mouse Bone Fracture Pain
 - Mouse Bone Cancer Pain

Neurotrophins, the Trk pathway and pain



- In inflammatory pain, NGF release is stimulated by cytokines such as IL-1 and TNF.
- Binding of NGF to TrkA on mast cells and neutrophils triggers amplification of the NGF signal and release of other pro-inflammatory mediators.
- Binding of NGF to TrkA on peripheral neurons triggers a profound pain response and also causes a post-translational change that results in BDNF release and activation of the BDNF/TrkB pathway.
- In the dorsal horn, BDNF binding to TrkB results in increased signaling through the NMDA, AMPA, mGlu and NK1 pathways and hypersensitization of peripheral neurons.

Inhibiting the Trk Signaling Pathway



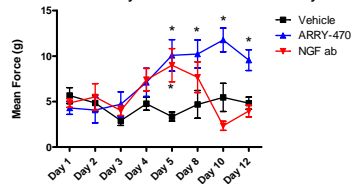
ARRY-470 is excluded from the brain by P-gp efflux

- At therapeutic doses 1-7% of the plasma concentration of ARRY-470 was measured in the brain
- Brain concentrations were increased in *mdr1a/1b/bcrp-/-* mice and in CF-1 *mdr1a* mutant mice

Selected *In Vitro* Properties of ARRY-470

Trk Family Cell IC ₅₀	TrkA = 6.5 nM TrkB = 8.1 nM TrkC = 10.6 nM
Kinase selectivity	No significant effects in a panel of 230 kinases @ 1 μM
Broad receptor panel selectivity	No significant effects in a panel @ 10 μM
CYP Inhibition (3A4, 2D6, 1A2, 2C9, 2C19)	IC ₅₀ > 25 μM
HERG (IC ₅₀)	IC ₅₀ > 10 μM
Genotoxicity testing	non-mutagenic non-clastogenic

ARRY-470 Demonstrates Sustained Inhibition of Mechanical Allodynia in a Chronic Inflammatory Pain Model



*p<0.05 by Two-Way ANOVA with Bonferroni's post-hoc test

Day 1 is Day 5 post-CFA injection ARRY-470 given BID on days 5-16. Single anti-NGF dose given on day 5

Figure 1
a) Animals received a single intraplantar injection of CFA 5 days prior to treatment with ARRY-470 or NGF antibody. Mechanical allodynia was confirmed before treatment with compounds. Beginning on day 5 post-CFA, ARRY-470 was delivered by oral gavage (BID, 30 mg/kg) and dosing continued through day 16. NGF antibody was delivered as a single IP injection on day 5 post-CFA. Mechanical allodynia was determined daily for the 12 days of the study.
b) In this chronic pain model, ARRY-470 brought pain-relief superior to NGF antibody, and its analgesic effect was sustained through the duration of the study. In addition, ARRY-470 has also demonstrated equivalent or superior analgesic activity in this model when compared to a high dose of indomethacin (not shown).

ARRY-470 is efficacious in a rat model of inflammatory pain (CFA) When dosed prophylactically or therapeutically

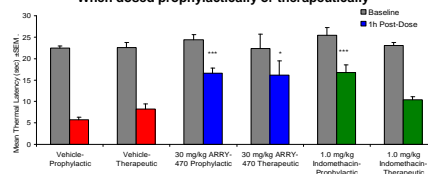


Figure 2
CFA was injected into the hind foot pad of Sprague Dawley rats. ARRY-470 was delivered 1 hour prior to injection of CFA for prophylactic dosing or 1 hour after CFA injection for therapeutic dosing. Thermal hyperalgesia was determined 1 hour after the last dose of ARRY-470.

ARRY-470 Has Superior Efficacy Compared To Standard NSAID Controls In A Rat Model Of Osteoarthritis

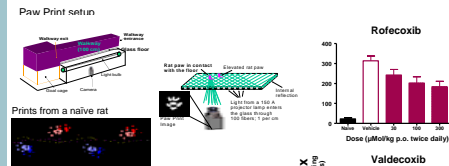
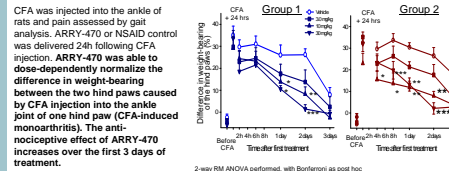
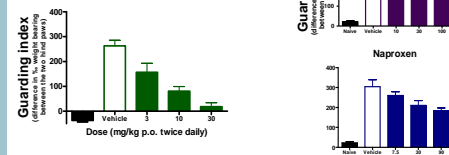


Figure 3 ARRY-470



Low-dose ARRY-470 inhibits thermal hyperalgesia for up to 12h

ARRY-470 3.0 mg/kg

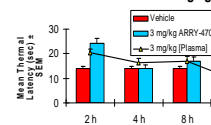
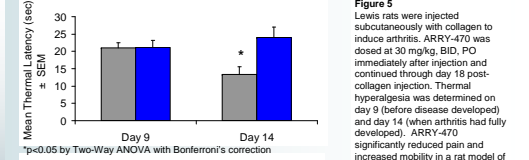
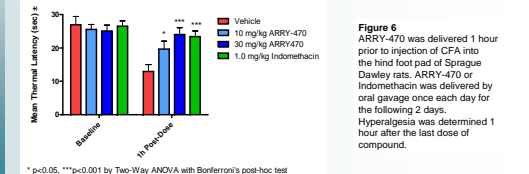


Figure 4
Inflammatory pain was induced by intraplantar injection of CFA in Sprague Dawley rats. Drug treatment was initiated 1 hour prior to CFA injection and continued twice daily for the subsequent 2 days. Mean thermal latency was determined by Hargreave's method at indicated times following the last dose on day 2.

ARRY-470 Inhibits Thermal Hyperalgesia in a Rat Collagen-Induced Arthritis Model



Once Daily Dosing of ARRY-470 Inhibits Thermal Hyperalgesia Equivalent to Indomethacin



Summary

- ARRY-470 is a highly selective and potent inhibitor of the Trk signaling pathway.
- ARRY-470 has drug-like properties and is bioavailable across preclinical species.
- ARRY-470 has a brain-to-plasma ratio of 0.02-0.10, suggesting its activity is peripherally mediated.
- ARRY-470 has demonstrated significant efficacy in many animal models of pain.
- ARRY-470 has proven to have a good profile of safety, both in general and specifically with respect to nerve health.
- Small molecule Trk inhibitors have potential benefit for the clinical treatment of pain.

References

1. Heffl, F. et al. (2006) Trends in Pharmacological Research: Feb. 27(1):85-91.
2. Dinah, Y. et al. (2006) Drug Dev Res 67(4):388-403.