ARRY-797, A SMALL MOLECULE p38α INHIBITOR, HAS A GOOD SAFETY PROFILE AND PROVIDES PAIN RELIEF IN CLINICAL STUDIES

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ABSTRACT

Aim: ARRY-797 is a potent, oral, highly selective p38α inhibitor. In initial clinical studies, it was shown that ARRY-797 decreases production of PGE2, as well as cytokines such as TNF and IL-1, in blood samples stimulated ex vivo. Because of this effect on PGE2, we undertook additional safety and PK studies in normal volunteers as well as studies of pain relief in dental and ankylosing spondylitis (AS) patient populations.

Methods: Safety and PK of ARRY-797 were assessed in a randomized, double-blind, placebo-controlled study in healthy subjects, with ascending doses of 200, 300 and 400 mg/day TID (q8h) for 8 consecutive days. In two acute dental pain studies, ARRY-797 was administered either prior to surgery or at the onset of moderate to severe pain. Total pain relief was measured over 6 hours following dosing. Additional endpoints were CRP, second dose benefit, time to onset of analgesia and total pain intensity. In a small study, ARRY-797 was administered to patients with active AS, with various disease and pain outcomes measured.

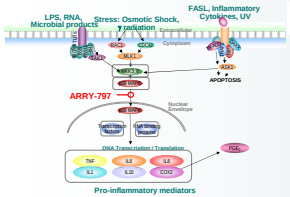
Results; Safety and PK: Based on the low incidence of adverse events (AEs), ARRY-797 was considered safe and well-tolerated following multiple-day administration of total daily doses of 600 mg, 900 mg, and 1200 mg. No clinically significant changes in clinical laboratory values, ECG, or vital sign assessments were observed. No AE was reported by more than 1 subject in any treatment group after multiple-day dosing; all were considered mild in intensity. Mean ARRY-797 plasma concentrations reached steady state on Day 2 after repeat-dose administration, with modest accumulation and slightly longer mean t1/2 values. Approximately dose-proportional increases in mean total and peak exposures were observed.

Results; Efficacy: In one dental pain study, ARRY-797 treatment regimens (pre- and post-surgery) produced a reduction in postsurgical pain intensity vs. placebo. ARRY-797 also reduced CRP levels on the day after surgery by 85%. In a second dental pain study, doses of ARRY-797 of 400 mg and 600 mg provided pain relief equal to the positive control, celecoxib 400 mg, in terms of onset, magnitude and duration. In patients requiring rescue 6-18 hrs following the first dose, a second dose of ARRY-797 200 mg resulted in greater analgesic benefit than placebo. In patients with active AS, there were improvements in disease and pain scores in patients receiving ARRY-797 100 and 200 mg BID, which endured over the 12-week treatment period.

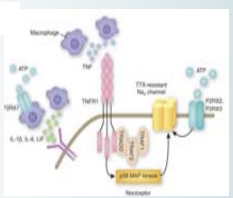
Conclusions: Based upon these clinical studies, ARRY-797 has proven safe and well-tolerated upon multiple days of dosing, at doses of up to 1200 mg/day. In addition, ARRY-797 has demonstrated signs of both acute and durable analgesic activity. ARRY-797 may provide a safe and orally-effective treatment for a variety of acute and sub-chronic inflammatory pain disorders.

INTRODUCTION

- ARRY-797 is a selective, small molecule inhibitor of p38α-mitogen-activated protein (MAP) kinase
- p38 is an intracellular kinase activated by stress, tissue damage and inflammatory mediators
- p38 has a role in mediation of inflammation & pain
  - p38 inhibition suppresses the production of PGE2, CRP, and inflammatory cytokines with potential applications in:
    - Inflammation
    - Inflammatory pain
    - Neuropathic pain
    - Development of chronic pain
- Clinical conditions with inflammatory or neuropathic pain components may be well-suited to treatment with p38 inhibitors



Role of p38 in the production of PGE2 following various pathological insults



In addition to regulating the production of PGE-2, p38 mediates proinflammatory cytokine (TNFα, IL-1β, IL-6) release as well as downstream signaling in peripheral nociceptive neurons

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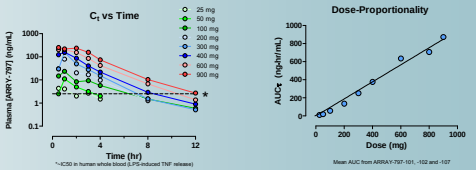
Clinical Experience – Safety

- In clinical safety studies of up to 14 days duration, ARRY-797, at doses up to 1200 mg/day
  - was generally safe and well-tolerated
  - had no effect on:
    - QTc or other ECG parameters
    - clinical chemistries, including liver enzymes
    - vital signs, including blood pressure
- In all clinical studies to date:
  - 371 subjects/patients have received at least 1 dose of ARRY-797 in doses up to 1,200 mg per day and for durations up to 12 weeks
  - The majority of adverse events were mild to moderate in severity
  - No treatment-related serious adverse events were reported
  - One SAE was reported in ARRY-797-201 (ankylosing spondylitis) in which a patient was diagnosed with Crohn's Disease; the event was assessed as not related to study drug
  - No deaths occurred while on study or within 30 days of last dose of study drug
  - No trends in safety data were noted

Clinical Experience – PK / PD



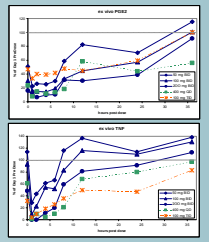
Pharmacokinetic Assessment

- Tmax ~1 hour after dosing
- Exposure increases with increasing dose
- Elimination rate independent of dose

ARRY-797 provided a significant and sustained PD effect

ARRY-797 was dosed for 13 days on the indicated schedule – the data displayed are for day 14, after the last dose, normalized to the pre-dose value.

Study: ARRY-797-102



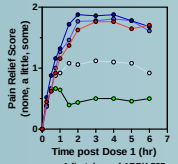
PK / PD Relationship

- Good correlation between PK and PD
- Significant inhibition of biomarkers was observed in the low ng/mL range
- Values similar to those observed *in vitro* and are in agreement with the low protein binding of ARRY-797

Clinical Experience – Pain

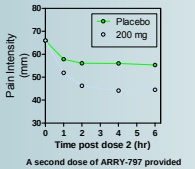
Dental pain - Two randomized, double-blind, placebo-controlled studies

- Study 1 (ARRAY-797-221; 68 subjects receiving ARRY-797)
  - 200 mg preoperative then 200 mg postoperative
  - 400 mg postoperative
- Study 2 (ARRAY-797-222; 157 subjects receiving ARRY-797)
  - 1 or 2 doses of ARRY-797 (200, 400 or 600 mg preoperative; 200 mg second dose)
  - Celecoxib comparator



A first dose of ARRY-797 provided significant pain relief compared to placebo

Study: ARRY-797-222



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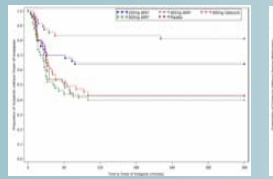
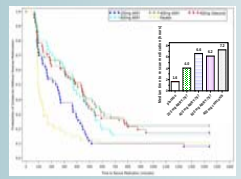


Time to Onset of Analgesia

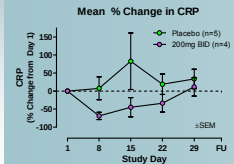
Study: ARRY-797-222



Time to Receipt of Rescue Medication Comparable to Celecoxib 400 mg

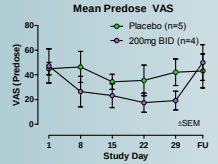
Study: ARRY-797-222

ARRAY-797-103 – 28-day RA Study: CRP and Pain (VAS)



% Change in CRP compared to baseline

As cited for other p38 inhibitors, the beneficial effects of p38 inhibition on most RA parameters wane over 28 days in RA patients



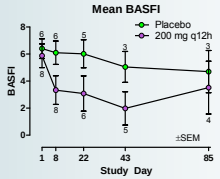
Pre-dose VAS values (0 – 100mm scale) on indicated study days [FU = Follow-up visit]

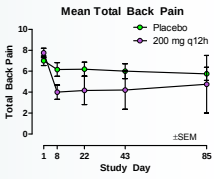
Only patients with a VAS ≥20mm at Pre-dose at Day 1 included

Clinical Experience – Pain

ARRAY-797-201 – 12-week study in patients with ankylosing spondylitis (AS)

- A randomized, double-blind, placebo-controlled pilot study
- Cohorts: placebo, 100 mg BID, 200 mg BID, 400 mg QD
- 25 patients randomized: 6, 4, 8, 7, respectively
- Analysis of patient responses suggests potential for efficacy on functional (BASFI) and pain endpoints with the 200 mg q12h dose





CONCLUSIONS

Based upon these clinical studies:

- ARRY-797 has proven safe and well-tolerated upon multiple days of dosing, at doses up to 1200 mg/day
- ARRY-797 has demonstrated signs of both acute and durable analgesic activity
  - Dental pain
    - Pain relief and onset comparable to celecoxib
  - Signs of activity on pain (VAS) in 28-day rheumatoid arthritis study at 200 mg BID
    - Small study not designed or powered to evaluate this endpoint
    - Sustained over 28 days with return to baseline at follow-up visit
  - From AS study, signs of activity on function (BASFI) and pain (nocturnal pain and total back pain) in a subset
    - Early termination of study minimized statistical power
- Pain relief with a p38 inhibitor may require doses at the high end (>90%) of PD inhibition
- ARRY-797 may provide a safe and orally-effective treatment for a variety of acute and sub-chronic inflammatory pain disorders

References

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