Results: The study is ongoing and full data will be presented at the meeting. Authors are presently blinded to the treatment arms. During the first 45 days of the study, only mild treatment-related adverse events were reported. Clinically relevant laboratory or ECG abnormalities have not been observed.
Conclusion: Up to this point, results of Phase 1 suggest that LBR-101 is well tolerated when delivered either IV or SC. Overt safety concerns have not emerged. Updated assessment will be presented at the time of the meeting.

P39
LBR-101 is not Associated with Signs of Liver Toxicity in Healthy Volunteers: Results of the Phase 1 Program
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Objectives: To characterize the hepatic effects of LBR-101, a monoclonal antibody against CGRP, by presenting the pooled results from the Phase 1 program.
Background: The potential role of CGRP in migraine pathophysiology was suggested more than 20 years ago and since then our knowledge of the peptide and its role in the pathophysiology of migraine has increased substantially, leading to a robust interest in targeting CGRP to treat migraine. Clinical proof-of-efficacy for the acute treatment of migraine has been obtained with several small molecule CGRP receptor antagonists, but their development has been complicated by signs of liver toxicity associated with frequent use. The utility of monoclonal antibodies as therapeutics includes target-specificity, as well as reduced potential for hepatotoxicity and drug-drug interactions.
Methods: Herein we report the pooled results of the Phase 1 program for LBR-101, which consisted of five studies testing intravenous (IV) administration, and one study testing including subcutaneous (SC) administration. All studies were double-blind, placebo-controlled trials enrolling healthy volunteers. Doses ranged from 0.2 mg to 2,000 mg given once, or up to 300 mg given twice (Day 1 and Day 14). The half-life of the drug is approximately 45 days. LBR-101 was given to 118 healthy subjects, while 57 subjects received placebo. Participants were confined in research units for at least 7 days, and followed for at least 90 days after drug administration. Laboratory tests included serum chemistries, hematology, and urinalysis. Hematology, chemistry, coagulation, and urine safety laboratory tests were performed at multiple study times.
Results: Clinical laboratory findings were similar across placebo and LBR-101. In particular, liver function abnormalities, defined as any post-dose value ***outside the normal test range,*** were not observed in subjects receiving any of the studied doses of LBR-101 within the following tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and gamma-glutamyl transferase (GGT) . Limited effects on liver function tests were seen in three patients receiving placebo. Clinically significant abnormalities were not seen for any other laboratory test.
Conclusion: LBR-101 does not seem to be associated with any signs of liver toxicity or with relevant changes in other laboratory findings.

P40
The Place of Corticosteroids in Migraine Management: Systematic Review and Critical Appraisal
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Objectives: To determine the role of corticosteroids in the management of migraine.
Background: Incomplete pain relief, repeated emergency department (ED) visits, and lost productivity contribute significantly to migraine-related economic burden. Headaches recur in up to 87% of migraine patients visiting ED, making ED recidivism a management challenge. Lower headache recurrence is a primary goal according to patients. Corticosteroids have long been used to optimize migraine management, even prior to current evidence demonstrating the significance of sterile neurogenic inflammation in migraine pathophysiology.
Methods: We conducted systematic review of clinical studies on corticosteroids for migraine from 1980 till date. PubMed search was employed for Clinical Studies Categories and Systematic Reviews on PubMed Clinical Queries tool combining the terms 'migraine' and 'corticosteroids'. References were searched to extract related published clinical studies.
Results: Twenty clinical studies and 4 systematic reviews were included. Eighty percent of the studies were randomized controlled trials conducted in ED settings. Migraine diagnosis was met by employing the International Classification of Headache Disorders criteria in 65% of the studies. Ninety percent of the studies indicated observed outcome differences favoring benefits of corticosteroids. Mean absolute risk reduction (ARR) was 27.6% (range 6%-48.2%; median 30%) and 18.6% (range 6%-48.6%; median 11%) for 24-hour and 72-hour headache recurrence, respectively. Parenteral dexamethasone was the most commonly (65%) used corticosteroid. Dexamethasone was administered with average single dose of 12.8mg (range 4-24mg; median 10; mode 8, 10mg) in 70% of the studies. All systematic reviews and meta-analyses revealed importance of adjuvant corticosteroids to various abortive medications – indicating generalizability of results. Three meta-analyses showed that a single dose of adjuvant parenteral dexamethasone was associated with 11.1% ARR, number needed to treat of 9, and 26% relative risk reduction for 72-hour headache recurrence. The fourth meta-analysis indicated that parenteral dexamethasone delivered highest efficacy. Adverse effects were tolerable. Higher disability, prolonged migraines, status migrainosus, incomplete pain relief, and headache recurrence were the settings where corticosteroids were beneficial. Abortive medications which were ineffective prior to dexamethasone became effective subsequently.
Conclusion: The use of corticosteroids in Migraine is inconsistent and controversial. Our literature review suggests that with corticosteroids, recurrent headaches become milder than pretreated headaches and later respond to nonsteroidal therapy. Intravenous dexamethasone provides reasonable option for the treatment of resistant, severe, or prolonged migraines. Dexamethasone restores

sensitivity to other abortive agents. Recommendations include 6-8 dexamethasone administrations per year with follow up of adverse effects. By virtue of having a half-life of 36-72 hours and being potent anti-inflammatory with negligible mineralocorticoid effect, dexamethasone suppresses inflammation during the period when patients are most likely to experience headache recurrence, potentially making it ideal for a one-time administration before ED discharge.

P41

Cognitive Behavioral Therapy Plus Amitriptyline Improves Headache Frequency to ≤ 3 Per Month in Children and Adolescents with Chronic Migraine

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Objectives: Determine if cognitive behavioral therapy plus amitriptyline (CBT+A) compared to headache education plus amitriptyline (HE+A) for chronic migraine leads to improvement in headache frequency to ≤ 5 and ≤ 3 per 28 days.

Background: How much impact an intervention for chronic migraine has can be measured by the degree of change in headache frequency. Ideally for patients, treatment would reduce headache days to very few to zero occurences with no side effects. In a randomized clinical trial for children and adolescents with chronic migraine, CBT+A was superior to HE+A on reduction in the number of days per month with headache and migraine-related disability at the 20-week endpoint and 12-month follow-up (Powers et al., JAMA, 2013;310:2622-2630). CBT+A was also superior on the metric of a ≥ 50% reduction in headache days. More pronounced change can be measured by headache frequency that meets criteria for the initiation of preventive medication (i.e., "Need for Prevention"). "Need for Prevention" has been defined (when based solely on frequency) as: Prevention medication should be offered: ≥ 6 per month; Medication should be considered: 4 or 5 per month; Medication not indicated: ≤ 3 per month (Lipton et al., Neurology, 2007;68:343-349). In our pediatric Headache Center, the clinical guideline is to suggest preventive medication if headache frequency is 4 or more per month. Thus, a benchmark of | 3 per month would indicate substantial improvement.

Methods: Randomized clinical trial of CBT+A vs HE+A with treatment effects measured at baseline, 20 weeks (post-treatment), and follow-up (12 months post-treatment as final assessment). Headache days measured by 28-day, prospective diary. Analyses were conducted with Chi-square test for independence.

Results: Participants had 21 ± 5 headache days per month at baseline; all 135 had ≥ 15 per month.

53% of the CBT+A group had ≤ 5 headache days at 20 weeks (HE+A = 23%; $p < 0.001$);

75% of the CBT+A group had ≤ 5 headache days at 12-month follow-up (HE+A = 55%; $p < 0.05$).

32% of the CBT+A group had ≤ 3 headache days at 20 weeks (HE+A = 16%; $p < 0.05$);

61% of the CBT+A group had ≤ 3 headache days at the 12-month follow-up (HE+A = 40%; $p < 0.05$).

Conclusion: Cognitive Behavioral Therapy plus Amitriptyline was not only superior to Headache Education plus Amitriptyline on ≥ 50% reduction in headache days along with disability reduction to the mild to none range (JAMA, 2013), but also led to more participants falling below the clinically relevant "Need for Prevention" of ≤ 5 and ≤ 3 days per month. From a clinical perspective, reduction of headache frequency from a chronic level to less than one per week is a major improvement. Our results demonstrate that CBT+A lowers headache frequency to a level that preventive medication is no longer needed as part of a multidisciplinary treatment plan. Next steps are to find effective ways to disseminate this high-impact treatment and to examine the trajectory of this improvement into early adulthood.

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P42

Breath-Powered™ Nasal Delivery of Powdered Sumatriptan (AVP-825): Migraine Disability and Functional Outcome in a Phase 3 Study (TARGET)

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Objectives: Migraine is associated with substantial disability; early treatment is critical to improving patient outcomes. AVP-825 is a first-in-class treatment for migraine, using a novel closed-palate Breath Powered™ device to deliver low-dose sumatriptan powder deep into the nasal cavity beyond the nasal valve—an area extensively innervated by the 1st and 2nd branches of the trigeminal nerve—where it can be rapidly and efficiently absorbed. In a Phase 3 trial (TARGET), 42% of patients using AVP-825 vs. 27% placebo reported headache relief by 30 min (P=.03), with 68% vs. 45% reporting headache relief at 2 h (P=.0016; primary outcome) and minimal triptan-related adverse effects. Here, key secondary outcomes from the AVP-825 TARGET study are reported to provide a clinical picture of migraine disability and associated functional improvement in these patients.

Methods: The TARGET study was a randomized, double-blind, placebo-controlled trial evaluating AVP-825 for the acute treatment of moderate or severe migraine headache. Patients were instructed to treat the first migraine headache following randomization as soon as headache reached moderate to severe intensity. Efficacy assessments were made immediately before dosing and at multiple time points up to 2 h after administration. The Headache Impact Test (HIT-6; a measure of disability) was assessed at baseline.