2. SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**
Study Title A Phase IIA, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Sequential Cohorts, Dose Range Finding Study to Evaluate the Safety, Tolerability and Clinical Effect of Escalating Doses of Laquinimod in Active Moderate to Severe Crohn's Disease	
Study Principal Investigators Geert D'Haens, MD PhD Academic Medical Center Meibergdreef 9 Amsterdam, The Netherlands	
Study Site Investigators and Respective Study Sites A total of 37 sites, with their respective 37 site investigators participated in the study.	
Publication Based on Study Results None	
Study Dates November 2008-November 2011	**Clinical Phase** IIa
Test Drug, Dose and Mode of Administration, Batch Number Laquinimod sodium, 0.5, 1.0, 1.5, and 2.0 mg, oral. Batch number: K-40346 and K-44082 **Reference Drug, Dose and Mode of Administration, Batch Number** Matching placebo. Batch number: K-40647, K-44094 and K-41992	
Objectives This study was exploratory in nature; therefore, no formal hypothesis testing was planned. The study objectives were: ▪ To evaluate the safety and tolerability and determine the highest tolerable dose of laquinimod (up to 2.0 mg/day), in subjects with active moderate to severe CD. ▪ To evaluate the clinical effect and dose response of laquinimod (0.5-2.0 mg/day), in subjects with active moderate to severe CD.	
Methodology This was a randomized, double-blind, placebo-controlled, sequential cohort, dose range finding study to assess the safety, tolerability, and clinical effect of escalating doses of laquinimod in subjects with active moderate to severe CD. Laquinimod doses of 0.5, 1.0, 1.5, and 2.0 mg daily were studied sequentially in distinct cohorts. Within each cohort, eligible subjects were randomized in a 2:1 ratio to receive either oral laquinimod (approximately 30 subjects) or matching oral placebo (approximately 15 subjects). Progression to successive cohorts was dependent upon randomization of at least 45 subjects for the preceding cohort and closure of screening and randomization for the preceding cohort, and the decision of a safety committee to proceed to the next dose level.	

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

Each cohort (dose group) was evaluated for up to 14 weeks: screening, between 1-2 weeks; treatment period, 8 weeks; and follow-up, 4 weeks. Scheduled in-clinic visits were conducted at screening, baseline and at Weeks 1, 2, 4, 6, and 8 post-randomization. Treatment with laquinimod/placebo was discontinued on visit Week 8 post-randomization and a follow-up/study completion visit was conducted at Week 12 post-randomization.

Number of Subjects (total and for each treatment):
A total of 180 subjects with CD participated in the study in 4 cohorts; 63 subjects were randomized to receive placebo, and 117 were randomized to receive laquinimod (29, 30, 29, and 29 subjects received laquinimod 0.5, 1.0 1.5, and 2.0 mg doses, respectively).

Diagnosis and Main Criteria for Inclusion
Inclusion:

- Males and females 18-75 years old (inclusive).
- Subjects diagnosed with CD for at least 3 months prior to screening, which had been appropriately documented and supported by endoscopy or radiology (performed within 36 months prior to screening and after surgical resection), or surgery.
- Moderate to severe CD patients as determined by a Crohn's Disease Activity Index (CDAI) score of 220-450 (inclusive).
- Subjects with C-reactive protein (CRP) levels above 5 mg/L at screening or any time between screening and baseline, including at baseline or documented endoscopic evidence of mucosal ulcerations within 4 weeks prior to baseline.
    - Evidence of mucosal ulcerations was defined as the presence of at least 2 ulcers ≥10 mm.
    - Documentation was to include the endoscopy report with supporting photo or video.
- Subjects willing and able to provide written, informed consent.

Exclusion:

- Subjects with a diagnosis of indeterminate colitis.
- Subjects with positive results on stool culture for enteric pathogens (Salmonella, Shigella, Yersinia, Campylobacter or *Clostridia difficile* toxin assay) at screening.
- Subjects who had bowel surgery within the 3 months prior to screening or with planned elective surgery or hospitalization during the course of the study (that may have interfered with study compliance or outcome).
- Subjects with clinically significant short bowel syndrome.
- Subjects with clinically significant GI obstructive symptoms.
- Subjects with intra-abdominal abscess.
- Subjects with fistula with clinical or radiological evidence of abscess.
- Subjects with ileostomy, colostomy or who received parenteral nutrition.
- Subjects with a clinically significant or unstable medical or surgical condition that, in the

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

investigator's opinion, would have precluded safe and complete study participation.

- Subjects with a ≥2 × upper limit of normal (ULN) serum elevation of any of the following at screening: alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase or direct bilirubin.
- A QT corrected for heart rate (QTc) interval which was >500 msec.
- Subjects with history of any malignancy in the last year prior to screening, excluding basal cell carcinoma.
- Subjects treated with oral corticosteroids (eg, prednisolone/budesonide), who had initiated this treatment within less than 4 weeks prior to screening.
- Subjects treated with more than 20 mg/day of prednisolone (or equivalent) or budesonide >6 mg/day for CD at baseline, or whose corticosteroid dosage regimen was not stable for at least 2 weeks prior to baseline.
- Subjects treated with 5-ASA who were not on stable dose for at least 2 weeks prior to screening.
- Subjects treated with antibiotics for CD at screening who were not on a stable dose for at least 2 weeks prior to screening.
- Subjects treated with 6MP, azathioprine or methotrexate, who had initiated this treatment within 12 weeks prior to screening, or who were not on a stable dose for at least 6 weeks prior to screening.
- Subjects treated with anti-TNFs within 4 weeks prior to screening. The percentage of subjects previously treated with anti-TNF drugs was to be limited to approximately 60% of subjects randomized for each cohort. Prior to implementation of Global Amendment 2, subjects treated with anti-TNFs within 8 weeks prior to screening were excluded, and the percentage of subjects previously treated with anti-TNF drugs was to be limited to approximately 40% of subjects randomized for each cohort.
- Subjects treated with cyclosporine, tacrolimus, mycophenolate mofetil or thalidomide within 2 months prior to screening.
- Subjects treated with natalizumab within 6 months prior to screening.
- Subjects who had used any other investigational drugs within 3 months prior to screening.
- Use of inhibitors of cytochrome P450 (CYP) 3A4 within 2 weeks prior to baseline visit (1 month for fluoxetine).
- Use of amiodarone within 2 years prior to screening visit.
- Women who were pregnant or nursing at the time of screening, or who intended to be during the study period.
- Women of child-bearing potential who did not practice an acceptable method of birth control.
- A known drug hypersensitivity that would have precluded administration of the study drug, such as hypersensitivity to: mannitol, meglumine or sodium stearyl fumarate.
- Subjects unable to comply with the planned schedule of study visits and study procedures.

Duration of Treatment
Subjects received treatment for 8 weeks.

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

Criteria for Evaluation

Efficacy Measures:

- Efficacy variables were CDAI score, serum C-reactive protein (CRP) levels and fecal calprotectin levels.

Safety Measures:

- Adverse events (AEs), vital signs, physical examination, safety laboratory evaluations, electrocardiogram (ECG).

Pharmacokinetic (PK) Measures:

- Blood samples for PK analysis - 24-hour profile - were collected in a pre-defined subset of sites from subjects in all cohorts on Week 4.
- A single, predose sample was collected from all cohorts on Week 1 as part of steady state course assessment.

Population PK Study (PPK):

- Blood samples for PPK evaluation were collected at Weeks 2 and 8 from all subjects in all cohorts. A predose sample and a single sample at postdose time range within 0.5 to 6 hours were collected.

Statistical Methods

Data analysis sets:

The following data analysis sets were defined:

- Intent-To-Treat Analysis Set (ITT): Included all randomized subjects. In this population, treatment was assigned based upon the treatment to which subjects were randomized, regardless of which treatment they actually received.
- Modified ITT Analysis Set (mITT): Consisted of all subjects mentioned in the ITT excluding observations following treatment failure (TF), where TF was defined as any new medication/treatment (including surgery) for CD or dose increase not allowed by the protocol throughout the study period (including the study treatment period of 8 weeks and the follow-up period of 4 weeks) or, for the purpose of efficacy analysis, any early termination (ET) from the study.
- Per Protocol Set (PP): Consisted of all subjects who completed the treatment period of 8 weeks and did not exhibit major protocol violations.
- Safety Analysis Set (ST): Consisted of all randomized subjects who received at least 1 dose of study drug. In this set, treatment was assigned based upon the treatment actually received, regardless of the assigned treatment.

The mITT analysis set was the primary analysis set for efficacy. The ST was used for safety analyses.

Efficacy analysis:

The study was an exploratory study, therefore no formal hypotheses testing was performed. Efficacy descriptive statistics are presented for each laquinimod dose versus all placebo treated subjects pooled across cohorts (approximately 30 subjects per each laquinimod dose and total of approximately 60

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

subjects for placebo).

Safety descriptive statistics are presented for each laquinimod dose versus all placebo treated subjects pooled across cohorts, as well as for all laquinimod doses pooled.

Exploratory efficacy analyses were primarily descriptive:

- The proportions of subjects who were in clinical remission (CDAI <150) and were not TFs and the proportions of subjects who responded to treatment with a reduction of CDAI score by at least 100 points (responders 100) or by at least 70 points (responders 70) were tabulated and plotted as function of visits for each laquinimod dose and for pooled placebo.
- Mean CDAI scores and mean CDAI changes from baseline were tabulated for each visit.
- Kaplan-Meier estimates of the time to remission and the time to response 100 and response 70 for the pooled data from all cohorts were presented using a survival curve stratified by treatment dose.
- Baseline adjusted Logistic regression was performed to assess the treatment effect on the proportion of subjects in remission at Week 8. Treatment dose entered the model as a categorical variable, and the covariates included in the model were: CDAI score at baseline, use of anti-TNF drugs in last year, current treatment with oral glucocorticosteroids (GCS), and current treatment with immunosuppressive drugs.
- A baseline adjusted Logistic regression similar to that used to assess the treatment effect on the proportion of subjects in remission at Week 8 was used to assess the treatment effect on the proportion of responders 100 and responders 70 at Week 8. The same covariates were included in the model.
- Mean levels and mean percent of change from baseline for CRP levels and fecal calprotectin levels were plotted and tabulated for each visit. For subjects who were TFs, the CRP/fecal calprotectin levels at LOV were carried forward for the purpose of the analysis of the mITT analysis set.
- The proportions of TFs any time during the study treatment period of 8 weeks (not including treatment termination date), and during the follow-up period of 4 weeks (including treatment termination date) were summarized descriptively.

***Post hoc* analysis:**

Post hoc analyses included:

- Sub-cohort analyses for remission, responders 100 and responders 70 (by previous use of anti TNF agents (separately according to data from Interactive Voice Response System and remote data capture systems), by oral GCS or immunosuppressive drugs at Baseline, by disease type (as assessed by the investigators), and by previous surgery)
- Normalization of calprotectin (defined as a shift from ≥250 µg/g at Baseline to <250 µg/g at Week 8 and reduction by at least 50%)
- Normalization of CRP (defined as CRP <5 mg/mL at Week 8 where CRP had been ≥5 mg/mL at Baseline)
- Remission/response and normalization of calprotectin
- Remission/response and normalization of CRP

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

- TFs during the follow-up period for subjects who completed 8 weeks without TF
- Change from Baseline in CDAI score

Summary of Results

Subject Disposition:
A total of 180 subjects with CD participated in the study (from Belgium, France, Israel, Italy, Netherlands, Poland, South Africa, Spain and the UK) in 4 cohorts; 63 subjects (35.0%) were randomized to receive placebo (across the 4 cohorts) and 117 subjects (65.0%) were randomized to receive 0.5, 1.0, 1.5, or 2.0 mg laquinimod doses (29 or 30 subjects per dose group).

The incidence of ET prior to Week 8 for the laquinimod 0.5, 1, 1.5 and 2 mg groups was 6/29 (20.7%), 6/30 (20.0%), 7/29 (24.1%) and 14/29 (48.3%) subjects, respectively, compared to 15/63 subjects (23.8%) in the pooled placebo group.

The most common reason for ET in all groups was AEs; the incidence of ET due to AEs was 10.3%, 10.0%, 17.2% and 41.4% in the 0.5, 1, 1.5 and 2 mg dose groups, respectively, and 12.7% in the pooled placebo group.

When Cohorts 1 to 4 were compared, regardless of treatment, a higher incidence of ET was noted in Cohort 4 in both laquinimod 2 mg and placebo arms compared to the other cohorts, but ET was more common in the laquinimod 2 mg arm (14/29 subjects [48.3%]) than in the placebo arm (6/16 subjects [37.5%]) within this cohort.

Demographics
Treatment groups were approximately balanced with respect to age and BMI; across all groups the mean age ranged between 35.1 and 40.9 years and mean BMI ranged between 23.3 and 25.2 kg/m^2. The proportion of females in the pooled placebo group (42.9%) was lower than in the laquinimod groups (55.2% to 72.4%).

Baseline Characteristics - Crohn's Disease

Mean baseline values of CDAI were similar for all treatment groups. Median baseline CRP levels were lower for the 1 and 2 mg laquinimod groups (6.7 and 6.5 mg/L, respectively) compared to the other groups (between 15.1 and 21.3 mg/L), and standard deviation (SD) was high for all groups (range 19.6 to 29.9 mg/L). Median baseline levels of fecal calprotectin were higher for the pooled placebo, 0.5 and 1 mg laquinimod groups (475.0, 468.0, and 543.0 μg/g, respectively) compared to the 1.5 and 2 mg laquinimod groups (318.0 and 270.0 μg/g); variability was very high, with SD ranging from approximately 800 to 1800 μg/g.

Approximately half of the subjects (92/180 subjects, 51.1%) had previously undergone any type of surgical treatment for CD, most commonly ileocolic resection (50 subjects, 27.8%). The incidence of

Name of Sponsor/Company:	**Protocol No.: CD-LAQ-201**
Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	

subjects who had undergone an ileocolic resection was lower in the laquinimod 0.5 mg dose group (10.3%) compared to all other treatment groups (between 22.2% and 41.4%).

Overall, more than half of all subjects had predominantly inflammatory (non-stricturing and non-penetrating) disease (100 subjects [55.6%]), with the highest incidence in the laquinimod 0.5 mg group (22 subjects [75.9%]).

Efficacy Results(based on mITT analysis set):

Clinical Remission

At Week 8, the proportion of subjects in clinical remission was higher for the laquinimod 0.5 and 1 mg groups, 14/29 subjects (48.3%) and 8/30 subjects (26.7%), respectively, compared to the higher dose laquinimod 1.5 and 2 mg groups, 4/29 subjects (13.8%) and 5/29 subjects (17.2), respectively, and the pooled placebo group, 10/63 subjects (15.9%). When adjusted for covariates, the lower bound of the 95% CI for the odds ratio of subjects in clinical remission at Week 8 in the laquinimod 0.5 mg treatment group compared to placebo was above unity (odds ratio 3.3; confidence limits 1.1 to 10.0). For the other laquinimod dose groups, the confidence limits included unity.

Response 100 and Response 70

The proportion of subjects who were responders 100 and responders 70 showed similar trends to the proportion of subjects in clinical remission. At Week 8, the proportion of subjects who were responders 100 was higher for the laquinimod 0.5 and 1 mg groups, 16/29 subjects (55.2%) and 12/30 subjects (40.0%), respectively, compared to the higher (1.5 and 2 mg) laquinimod dose groups, 8/29 subjects (27.6%) for both groups, and the pooled placebo group, 20/63 subjects (31.7%). Similar results were observed for responders 70.

Time to Remission/Response

Subjects in the laquinimod 0.5 and 1 mg groups achieved clinical remission earlier than subjects in the pooled placebo group. The difference was apparent as early as 2 weeks post-baseline and increased steadily until Week 8. The extent of difference between the laquinimod 0.5 mg and pooled placebo group was larger than that for the laquinimod 1.0 mg group compared to pooled placebo, and remained consistent throughout the treatment and follow-up periods. No consistent difference was observed between the laquinimod 1.5 mg and 2 mg treatment groups compared to the pooled placebo.

The laquinimod 0.5 mg dose showed an effect in reducing the time to response 100 compared to the pooled placebo; the difference was apparent from approximately Day 7 onwards, and was consistent throughout the treatment and follow-up period. The laquinimod 0.5 and 1 mg doses showed an effect in reducing the time to response 70 compared to the pooled placebo, and the separation between the curves started around Day 28.

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

Sub-Cohort Analyses

Sub-cohort analyses were performed by previous use of anti-TNF agents (separately according to remote data capture [RDC; during the past year] or IVRS [Interactive Voice Response System; any time in the past]), by use of oral GCS or immunosuppressive drugs at Baseline, by disease type, and by previous surgery. Some of the subgroups were small, and hence the proportions were sensitive to the small sample size; nevertheless the effect of laquinimod 0.5 mg was consistent.

CDAI Score

A decrease in mean CDAI score was observed for all treatment groups (including pooled placebo) at all time points, with the exception of the laquinimod 1 mg group at Week 1 in which mean CDAI was similar to the baseline value. The CDAI changes from Baseline were highly variable, with SD ranging from 83 to 148 at Week 8. For each group, these decreases in CDAI persisted to the follow-up, with similar values being observed at Week 12.

CRP and Fecal Calprotectin Levels

There was high inter subject variability in CRP data. At Week 8, for laquinimod 0.5 mg there was a mean % decrease from Baseline compared to a mean % increase for the other treatment groups. At Week 8, there was a median % decrease from Baseline for the laquinimod 0.5 mg and pooled placebo groups, with the decrease more marked for laquinimod 0.5 mg than pooled placebo, and a median % increase for the other groups.

There was high inter-subject variability in calprotectin data, with no evidence of any consistent treatment- or dose-related trends in the mean or median percent of change from Baseline. For subjects considered to be ‘at risk’ at Week 8 (defined as subjects with fecal calprotectin level ≥250 µg/g at Baseline and non-missing calprotectin level at Baseline and Week 8), a greater proportion had normalization of calprotectin levels at Week 8 (defined as a shift from ≥250 µg/g at Baseline to <250 µg/g at Week 8 and reduction by at least 50%) for the laquinimod groups (range 26.7% to 38.9%) compared to the pooled placebo group (13.6%).

At the end of Week 8, the proportion of subjects who satisfied both remission and normalization of fecal calprotectin levels was 27.8%, 16.7%, 6.7% and 18.2% in the 0.5, 1, 1.5 and 2 mg dose groups respectively, compared to 2.3% for the pooled placebo. Similar results were observed for the proportion of subjects who had normalization of fecal calprotectin and who were responders 100/responders 70.

Proportion of Treatment Failures

Any ET from the study was regarded as a TF. The rate of TF was higher for the laquinimod 2 mg group, 15/29 subjects (51.7%), compared to the 0.5, 1, and 1.5 mg groups, 6/29 (20.7%), 6/30 (20.0%), and 7/29 (24.1%) subjects, respectively, and the pooled placebo group, 17/63 subjects (27.0%).

Most TFs (100% of TFs in the laquinimod 0.5, 1, and 1.5 mg groups, 93.3% in the laquinimod 2 mg group, and 88.2% in the pooled placebo group) were ET.

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

Only 3 subjects that completed the study without ET had TF due to medications: 2/63 subjects (3.2%) in the pooled placebo group due to antibiotics and 1/29 subjects (3.4%) in the laquinimod 2 mg group due to GCS.

Pharmacokinetic Results:
Plasma concentrations of laquinimod increased after oral administration of laquinimod, reaching maximum levels within 1 hour after dosing in the majority of subjects, and plateauing thereafter with no clear terminal phase during the 24-hour dosing interval. Consistent with its known long half-life, repeated dose administration of laquinimod resulted in a predictable systemic accumulation. The predose and 24-hour concentrations on Week 4 were comparable in all cohorts confirming steady state conditions. Across the different dosing groups, the plasma concentrations of laquinimod on Week 4 generally increased with dose. Dose-normalized PK parameter values were comparable across the 0.5 to 2 mg dose range. Using the statistical model (analysis of covariance), the slope was not statistically significantly different from zero. The pharmacokinetics of laquinimod appeared linear in the dose range of 0.5 to 2 mg administered once daily to subjects with CD.

Safety Results:

Extent of Exposure

Median exposure to study drug was similar for all treatment groups (56 to 57 days); mean exposure was approximately 50 days for all groups except for laquinimod 2 mg, in which mean exposure was approximately 40 days. The lower mean exposure for the 2 mg group was due to the higher rate of ET in this group.

Adverse Events

The overall incidence of AEs was 86.2%, 96.7%, 89.7% and 89.7% for the laquinimod 0.5 mg, 1 mg, 1.5 mg and 2 mg doses, respectively, compared to 82.5% for the pooled placebo. There was no apparent dose response relationship for the overall incidence of AEs. Most AEs were mild or moderate in severity.

Common Adverse Events

Common AEs, defined as AEs (PT) reported by at least 10% of subjects in any laquinimod dose group and with a risk ratio over pooled placebo of at least 1.5 in any of the laquinimod dose groups or for which incidence on pooled placebo was zero. Headache was the most common AE in all treatment groups. The incidence of headache was higher in the laquinimod 2 mg group (44.8%) compared to the laquinimod 0.5, 1, and 1.5 mg groups (24.1% to 26.7%) and the pooled placebo group (20.6%). The incidence of abdominal pain in the 0.5 mg (17.2%) and 1 mg (13.3%) groups was similar to its incidence

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

in the pooled placebo group (12.7%), and lower than in the 1.5 mg and 2 mg groups (both 24.1%).

Serious Adverse Events

No subjects died during the study.

There was no apparent dose response relationship for the overall incidence of serious adverse events (SAEs), with incidence of 10.3%, 26.7%, 3.4%, and 10.3% in the laquinimod 0.5, 1, 1.5, and 2 mg groups, respectively, compared to 11.1% in the pooled placebo group. The most common SAE was CD (exacerbation) reported by 6.9%, 10.0%, 3.4%, and 3.4% of subjects in the laquinimod 0.5, 1, 1.5, and 2 mg groups, respectively, and by 1.6% of subjects in the pooled placebo group. Most other SAEs were reported by single subjects.

Adverse Events Leading to Early Termination

The overall incidence of AEs leading to ET (prior to completion of 8 weeks of treatment) was greater for the laquinimod 2 mg group (41.4%) compared to the other laquinimod groups (10.0% to 17.2%), in which the incidence was similar to the pooled placebo group (12.7%). Other than exacerbation of CD (cause of ET in 3.2%, 6.9%, 6.7%, 3.4%, and 6.9% of subjects in the pooled placebo and laquinimod 0.5, 1, 1.5, and 2 mg groups, respectively), the AE that most commonly led to ET was abdominal pain; this was the reason for ET in 1.6%, 3.4%, 0%, 3.4%, and 6.9% of subjects in the pooled placebo and laquinimod 0.5, 1, 1.5, and 2 mg groups, respectively.

Clinical Laboratory

There were no consistent trends in change from Baseline for any biochemical parameter in any of the dose groups or the pooled placebo group. Mean changes from Baseline for pancreatic amylase were consistently greater for all laquinimod dose groups compared to the pooled placebo group. Changes from Baseline to the upper PCS limit of 159 U/L for pancreatic amylase were infrequent, observed for 1 subject in each of the laquinimod 0.5, 1.5, and 2 mg groups only.

There were no consistent trends in change from Baseline for any hematological parameter in any of the dose groups or the pooled placebo group.

Vital signs and ECG

Vital signs and ECG findings were unremarkable. There were no clinically significant changes in vital signs or ECGs in the laquinimod dose groups.

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

Main Findings and Conclusion

- Laquinimod had a favorable safety and tolerability profile in subjects with active moderate to severe CD when administered for 8 weeks.
    - The overall incidence of AEs in the laquinimod dose groups ranged from 86.2% to 96.7%, comparable to the incidence of AEs in the pooled placebo group (82.5%).
    - Headache was the most common AE in all treatment groups. The incidence of headache was higher in the laquinimod 2 mg group (44.8%) compared to the laquinimod 0.5, 1, and 1.5 mg groups (24.1% to 26.7%) and the pooled placebo group (20.6%). The incidence of abdominal pain in the 0.5 mg (17.2%) and 1 mg (13.3%) groups was similar to its incidence in the pooled placebo group (12.7%), and lower than in the 1.5 mg and 2 mg groups (both 24.1%).
    - Most AEs were mild or moderate in severity. There were no deaths. There was no apparent dose response relationship for the overall incidence of SAEs, with incidence of 10.3%, 26.7%, 3.4%, and 10.3% in the laquinimod 0.5, 1, 1.5, and 2 mg groups, respectively, compared to 11.1% in the pooled placebo group.
    - The overall incidence of AEs leading to ET (prior to completion of 8 weeks of treatment) was greater for the laquinimod 2 mg group (41.4%) compared to the other laquinimod groups (10.0% to 17.2%), in which the incidence was similar to the pooled placebo group (12.7%).
    - There were no clinically significant changes in clinical laboratory, vital sign, or ECG data in the laquinimod dose groups.
- Laquinimod 0.5 mg had a robust and consistent therapeutic effect across all outcome measures and almost all subgroups.
    - 48.3% of subjects in the laquinimod 0.5 mg group were in remission at the end of the treatment period (Week 8), compared to 15.9% in the pooled placebo group. Similar results were observed for response 100 and response 70.
    - The effect of laquinimod 0.5 mg was noted as early as 2 weeks after initiation of treatment and was consistent throughout the subsequent treatment and follow-up periods.
    - The effect was consistent across subgroups, eg, by previous use of anti TNF agents (either recorded by IVRS [any time in the past] or by RDC [during the past year]), by use of oral GCS or immunosuppressive drugs at Baseline, by disease type, and by previous surgery.
- Laquinimod 1 mg had a lower magnitude effect that was also less robust than the effect of laquinimod 0.5 mg.
- There was no apparent dose response. Laquinimod 1.5 and 2 mg did not have an overall clinical effect compared to the pooled placebo.

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Hatrufa Street 12 Netanya 42504, Israel **Code Name of Finished Product:** TV-5600 (previously ABR-215062) **Name of Active Ingredients:** Laquinimod sodium	**Protocol No.: CD-LAQ-201**

- All laquinimod doses appeared to have an effect on normalization of fecal calprotectin.
- The pharmacokinetics of laquinimod appeared linear in the dose range of 0.5 to 2 mg. Repeated dose administration of laquinimod resulted in a predictable systemic accumulation.

Overall, results of this exploratory study suggest that daily laquinimod doses of 0.5 and 1 mg may have a positive risk-to-benefit ratio in patients with moderate to severe CD and support the continuing development of laquinimod for the treatment of CD.