Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Cahill KN, Katz HR, Cui J, et al. KIT inhibition by imatinib in patients with severe refractory asthma. N Engl J Med 2017;376:1911-20. DOI: 10.1056/NEJMoa1613125

Supplemental Appendix:

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Supplementary Methods:

Methacholine challenge

All asthma medications that could be safely withheld the morning of methacholine challenge were withheld e.g. oral glucocorticoids, leukotriene receptor antagonists (LTRAs), etc. Timing of medications that the patient could not withhold was noted so that the timing was reproduced each time the challenge was administered. Methacholine challenge has been performed safely in asthmatics with baseline FEV_1 as low at 55% (1). For the purposes of the KIA trial, the lower FEV_1% limit was set at 40%. Appropriate safety features were in place throughout the methacholine challenges including the presence of a study qualified medical personnel, immediate availability of emergency rescue medication, and reversal with inhaled bronchodilator at the completion of the challenge to within 10% of their pre-challenge FEV_1%. One severe adverse event that was attributed to methacholine challenge was reported in a patient with frequent glucocorticoid-requiring exacerbations maintained on oral glucocorticoids. A full methacholine challenge including reversal of FEV1 to within 90% of baseline was performed. One hour later the patient reported congestion and mucus. She increased her oral glucocorticoids that evening and 2 days later was admitted to the ICU for 2 days of treatment and was eventually discharged.

PC_{20} was determined using standard techniques (2, 3) up to a methacholine concentration of 25 mg/ml. Participants withheld their morning dose ($\geq$12 hour withhold) of inhaled glucocorticoids and long-acting bronchodilators and their short-acting beta-agonist dose for $\geq$6 hours. For those patients who failed to react at 25 mg/ml we had predetermined that we would extrapolate the value and truncate extrapolation at 100 mg/ml (1 imatinib extrapolated to 58 and 3 imatinib and 3 placebo truncated at 100). Bronchoscopy with endobronchial biopsy was performed as outlined in the supplement (Supplemental Appendix).

Allergy Skin Testing

Testing was performed after participants withheld their antihistamine for 1 to 7 days depending on the class. 10 allergen extracts (mite mix, coackroach, mouse, rat, penicillium mix, *alternaria alternata*, aspergillus mix, cat and dog at 1:20 w/v, *and cladosporium herbarum* at 1:40 w/v) from Greer Laboratories, Lenoir, NC plus positive histamine 10mg/ml and negative 50% glycerin controls were assessed at baseline, week 12 and week 17. The test was read at 15 minutes and largest wheal diameter and corresponding perpendicular diameter was measured in mm and mean diameter calculated. Participants with dermatographism, i.e. mean diameter of negative control $\geq$ 3mm, or FEV_1 below 50% predicted were excluded from testing.

Maximum Bronchodilator Response Testing

Asthma medications were withheld and participants performed 3 spirometry maneuvers 15 minutes after 2 puffs of albuterol were delivered via meter dose inhaler (MDI). The percent change in FEV_1 was calculated after each administration of albuterol to determine an albuterol dose response curve for each participant. This process was repeated up to a maximum of 8 puffs of albuterol or until the change in FEV_1 from baseline or prior post-bronchodilator value was ≤ 5%.

Peak Expiratory Flow (PEF)

PEF measurements were electronically recorded and date/time stamped from the AM1 device (Jaeger, Germany) (4). Participants are instructed to perform their morning and evening peak flow maneuvers right before taking their study medications.

Mast Cell Mediators

All urine samples were stored at -80^{o}C and analyzed by using gas chromatography–mass spectrometry. The stable cysteinyl leukotriene metabolite LTE_4 (5) and the major PGD_2 metabolite 9a,11b-dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid (PGD-M) (6) were measured and reported as picomoles per milligram of creatinine (Cr) in urine. Serum and BAL total tryptase levels were measured by UniCAP and ELISA respectively at Virginia Commonwealth University (7, 8). The stable cysteinyl leukotriene metabolite LTE_4 (5) and the major PGD_2 metabolite (PGD-M) (6) were measured and reported as picomoles per milligram of creatinine (Cr) in urine. BAL fluid was assessed for PGD_2, histamine, and cys-LTs (PGD2-MOX ELISA, histamine EIA, and cysetinyl leukotriene ELISA, Cayman Chemical, Ann Arbor, MI) according to the manufacturer's instructions after C18 column lipid purification (GE Healthcare, Pittsburgh, PA) as described previously (9).

Immunohistologic counting of MCs

Biopsies were fixed in 4% paraformaldehyde, embedded in paraffin, and 6 μm sections were prepared. Sections were incubated with 3% hydrogen peroxide to inactive endogenous peroxidases, Dako Target Retrieval Solution pH 9, and mouse anti-human tryptase mAb AA1 (Dako) at a concentration of 0.1 μg/ml or isotype control mouse IgG1 at the same concentration. Antibody binding was visualized with the DAKO EnVision+ System-HRP (AEC) system, and sections were counterstained with Gill's hematoxylin number 2 (Sigma). Sections incubated with the isotype control were negative for MC staining.

One blinded observer (HRK) counted the number and distribution of mast cells in endobronchial biopsies, measuring the numbers of mast cells in the ASM and total airway per millimeter $(mm)^2$ using immunoreactivity for tryptase in 6 μm paraffin sections(10, 11). For each patient visit, we analyzed a minimum total smooth muscle area of 0.1 mm^2 from at least two

sections, either from different biopsy fragments or at least 10 µm apart if from the same biopsy fragment. The coefficient of variation in mast cell counts was less than or equal to 5.5%.

For MC counts in muscle, muscle regions were delineated in photomicrographs and their areas were determined with Image J software, muscle MCs were counted on the photomicrographs with Image J, and the number of MCs was divided by the area of muscle analyzed. A single blinded investigator performed all mast cell enumerations. 10 randomly selected biopsies were recounted in a blinded fashion to assess for the coefficient of variation.

Total MC counts were done on the same biopsy specimens used for muscle MC counts. The total areas of the biopsies were determined in photomicrographs with Image J, MCs in the regions not already counted in the muscle analyses were counted, and the combined MCs counts were divided by the total areas of the biopsies.

Bronchial alveolar lavage cell counts

Cytospin slides of BAL cells were prepared and stained with Dif-Quick. Up to 200 cells per sample were analyzed.

Statistical analysis

Our primary outcome was change in airway hyperresponsiveness, as assessed by PC_{20}, from baseline to 3 and/or 6 months of therapy in imatinib treated participants as compared with controls. Change in PC_{20} was assessed using $\log_2$-transformed ratios of PC_{20} at month 3 and /or month 6 vs PC_{20} at baseline. Our null hypothesis was that the mean of this ratio will be 0 after $\log_2$-transformed. We used a linear mixed-effects model for a repeated-measures analysis to compare the primary outcome between the two groups. The statistical model was

$$Y_{ijk} = \mu_{ik} + \varepsilon_{ijk}$$

where Y_{ijk} is the response from the k^{th} study visit of the j^{th} participant within the i^{th} treatment group, μ_{ik} is the population mean for the k^{th} study visit within the i^{th} treatment group, and ε_{ijk} is the random error term, in which $\left[\varepsilon_{ij1}\ \varepsilon_{ij2}\ \ldots\ \varepsilon_{ijK}\right]^T$ follows a K-variate normal distribution with null mean vector and unstructured variance-covariance matrix Σ.

The primary analysis was performed for a modified per-protocol population, which included all randomly assigned participants for whom there was at least one post-baseline observation. Those without a post-randomization PC_{20} were not included. Our observed beta estimate for treatment was 1.29 (SE 0.64), p value = 0.0485. The treatment group on average had a 3.6-fold higher PC_{20} change relative to baseline, which represents a statistically significant change compared to the control group.

For FEV_1 we used a linear mixed-effects model to assess the between-group difference in the change from baseline over weeks 8-24. Any Participant that did not have at least one value reported after week 8 was not included in the analysis.

Bronchoscopy

Exclusion Criteria for Bronchoscopy Procedure

<u>The participant will not be eligible for the bronchoscopy procedure, if he/she meets any of the following criteria.</u>

1. Participant's pre-bronchodilator FEV_1 is < 40% predicted or < 85% of their study baseline
2. Participant has been hospitalized for asthma within the past 6 weeks
3. Participant required intubation for asthma within the past 6 months
4. Participant experienced > 12 asthma exacerbations within the past year
5. Participant needed to use > 16 puffs SABA per day in the past 48 hours
6. Participant experienced increased asthma symptoms requiring SABA use >8 puffs/day over baseline in the past 48 hours
7. Participant required an additional oral corticosteroid (OCS) or a doubling of OCS dose in the past 14 days
8. When required, the participant cannot arrange a caretaker to drive them home
9. Participants having URI in the past 14 days will require MD approval

Bronchoscopy Procedures

I. Biopsies

Biopsies should be performed first, followed by the brushings, and finally BAL at the end. Please see the flow diagram that follows. Before proceeding with biopsies, check forceps for proper function. The technician or nurse should be prepared to assist the physician in obtaining biopsies (if so requested). The instillations should be performed as per the following flow diagram. BAL is performed by instilling warmed (37^0C) sterile saline and collecting the fluid recovered into fresh 50 mL polypropylene tubes. During the BAL procedure, no air is introduced behind the lavage sample. BAL fluid is pooled into 1 or 2 50 mL polypropylene tubes based on the amount of sample. Return specimen tubes may need to be switched when full, and are collected on ice. If participant has difficulty with coughing, do not proceed to the bronchial wash.

When biopsies are taken, pull gently and consistently for best results. Do not pull quickly or jerk at the forceps. During collection, place each biopsy sample in the specific tubes until you obtain 8-10 acceptable samples. The samples should be put in the tubes according to their order of collection, i.e. the first acceptable sample collected is placed in the tube #1 and so on. The preferred order for samples is listed in the KIA Specimen MOP. Make sure that the location of each sample is known.

a. Evaluate the biopsy for acceptability according to criteria. Adequate biopsy specimen characteristics:

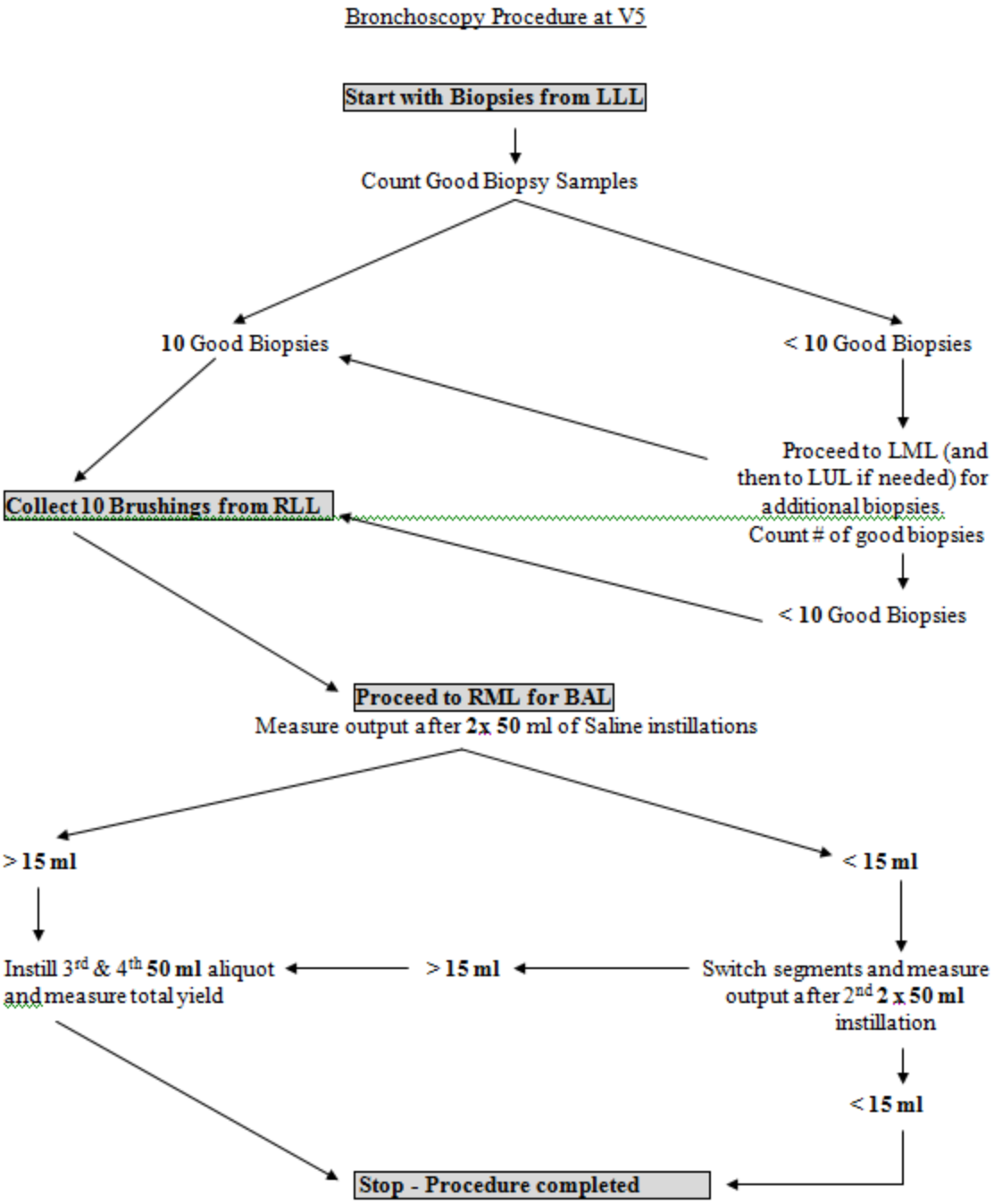
i. One piece (not several small pieces).
ii. Big as a pinhead (1-2 mm).
iii. White, not red (i.e. little blood as possible, although later biopsy pieces will likely to have more blood than the earlier ones).
iv. Non-cartilaginous. A biopsy with cartilage is usually bigger and less elastic than the one without cartilage.
v. Pieces should sink (*NOT float*) to the bottom of the collection tubes.
vi. If you feel the specimen is not adequate, place it in the appropriate solution, but inform the physician that he/she needs to obtain another sample.

b. If acceptable, write a "1" on the top of the tube of the first acceptable sample collected in permanent marker, record the location from where it was taken and place on ice.

c. If unacceptable, write an "X1" on the top of tube, record the collection site and place on ice.

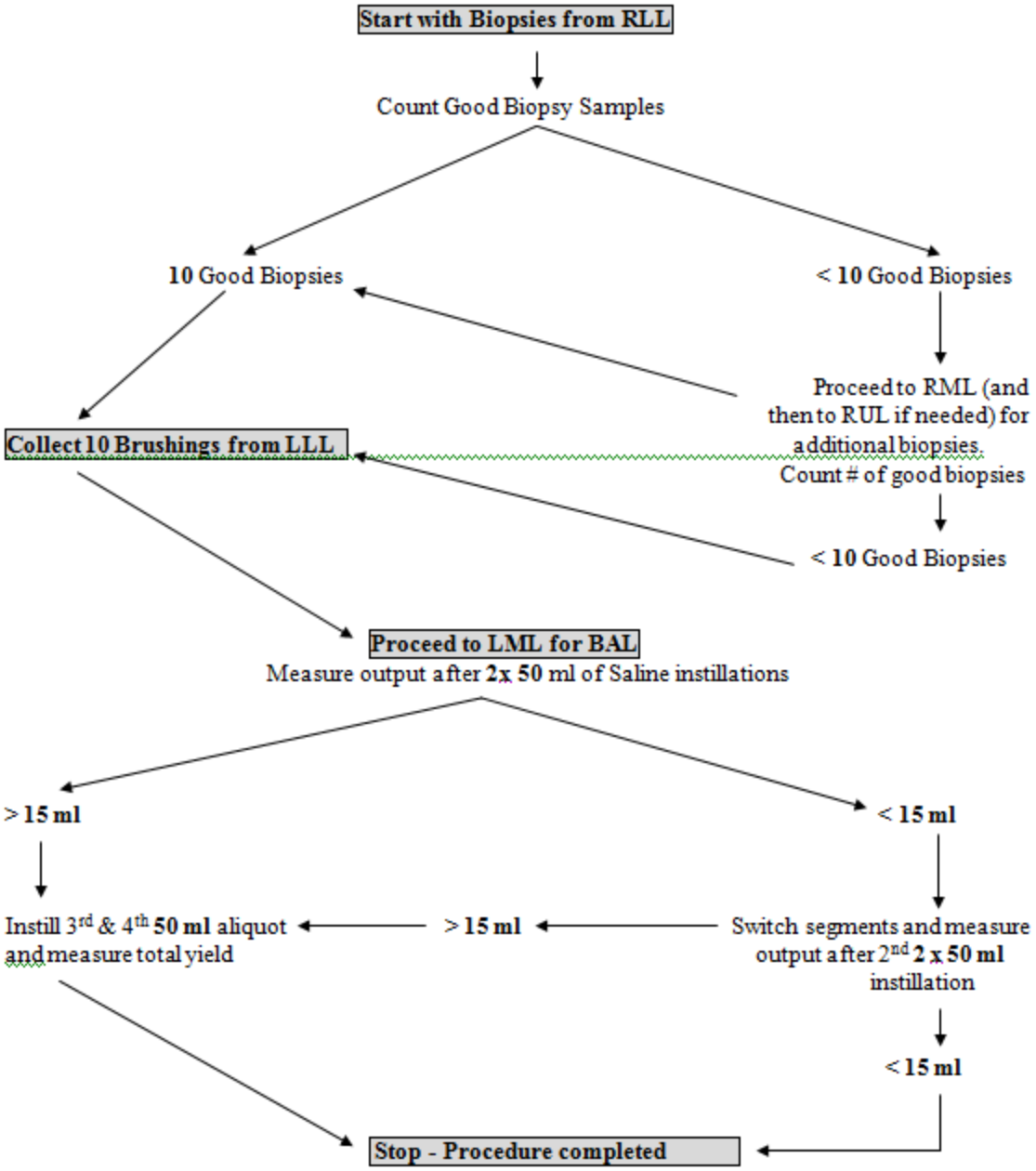
d. Subsequent acceptable biopsies should be marked "2", "3", "4", "5", "6", "7" and "8" sequentially and unacceptable biopsies "X2", "X3" and so on as they are taken.

Ten acceptable biopsy specimens are needed. Once the biopsy specimen is taken, the forceps should be given to the individual handling tissue. Consult Specimen Technician for quality.



Note: *During second bronchoscopy procedure, the sequences of procedures will remain the same, except we will switch the procedures performed on the left lung with the right lung. See following diagram.*

Bronchoscopy Procedure at V18



II. Brushings

Brushings should be taken after biopsies. Bronchial brushings should be performed from segments of the lung where you did not perform bronchial biopsy. Advance the BARD Disposable

Microbiology Brush into the segment and "drop" the plug. Advance the brush and gently brush the bronchial mucosa (about 0.5 to 1 inch) while rotating the brush 360^{o}. After about 10 seconds of brushing, retract the brush completely into the inner catheter. Then retract the inner catheter into the outer catheter by pulling the blue and white section apart. Withdraw the microbiology brush assembly from the bronchoscope. See description below on how to remove the brush. Collect additional microbiology brush samples.

Remove the brush sample by first wiping the outer catheter approximately 5 mm distal to the inner catheter with an alcohol prep (proposed cut site), and then cut the outer catheter at the alcohol cleansed site, and discard. Then, completely advance the inner catheter. Wipe the inner catheter about 5 mm distal to the brush tip (proposed cut site) with another alcohol prep, and then cut the inner catheter at the alcohol cleansed site. Advance the brush directly and completely into the 2.0 mL microtube containing RNALater™. Cut the wire level with the top of the tube, so that brush is kept fully immersed in the RNALater™. Screw the cap on tightly and place on ice. Be sure that the forceps do not contact the RNALater™.

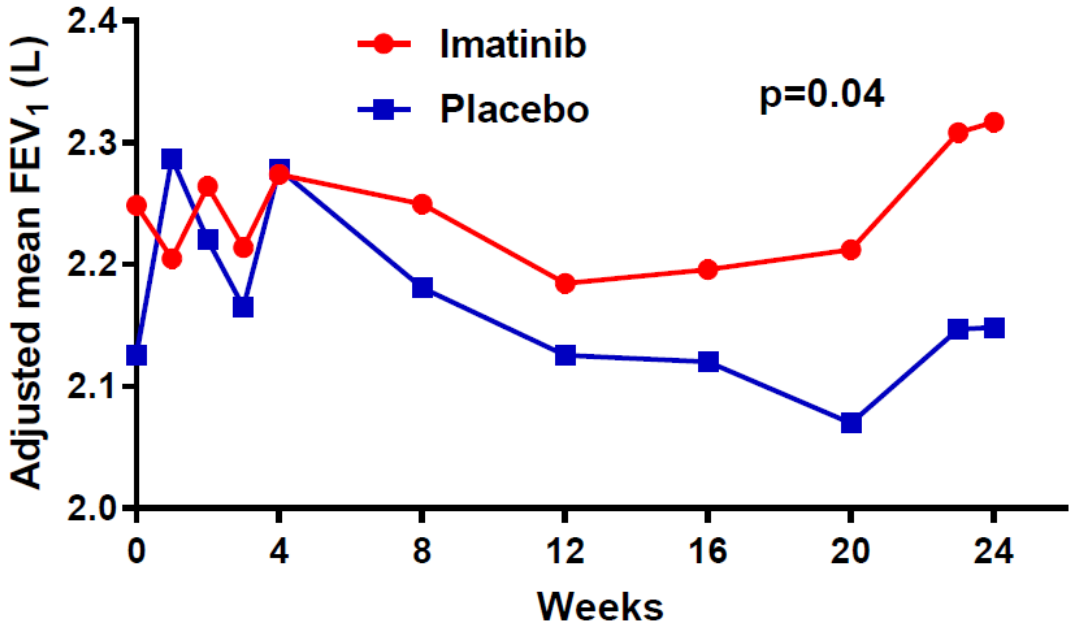
III. BAL

BAL will employ 50 ml aliquots. The standard technique will be instillation and recovery of one aliquot, followed by instillation and recovery of second aliquot. If the recovered volume is < 15 ml from the first two 50 ml injectates, then switch to another segment. If the recovered volume from the second segment is again < 15 ml after two 50 ml instillations, then BAL will be stopped. If the recovered volume from initial or second segment after two instillations is > 15 ml then instill the 3^{rd} and 4^{th} aliquot of 50 ml saline and measure the total return. The BAL procedure should be stopped after the 4^{th} instillation. The BAL return after all instillations will be pooled and measured. The total volume of BAL should be combined and quickly mixed to ensure consistency in the samples.

During second bronchoscopy procedure, the sequences of procedures as described above will remain the same, except we will switch the procedures performed in the right lung with the left lung and vice versa.

Supplemental Figures:

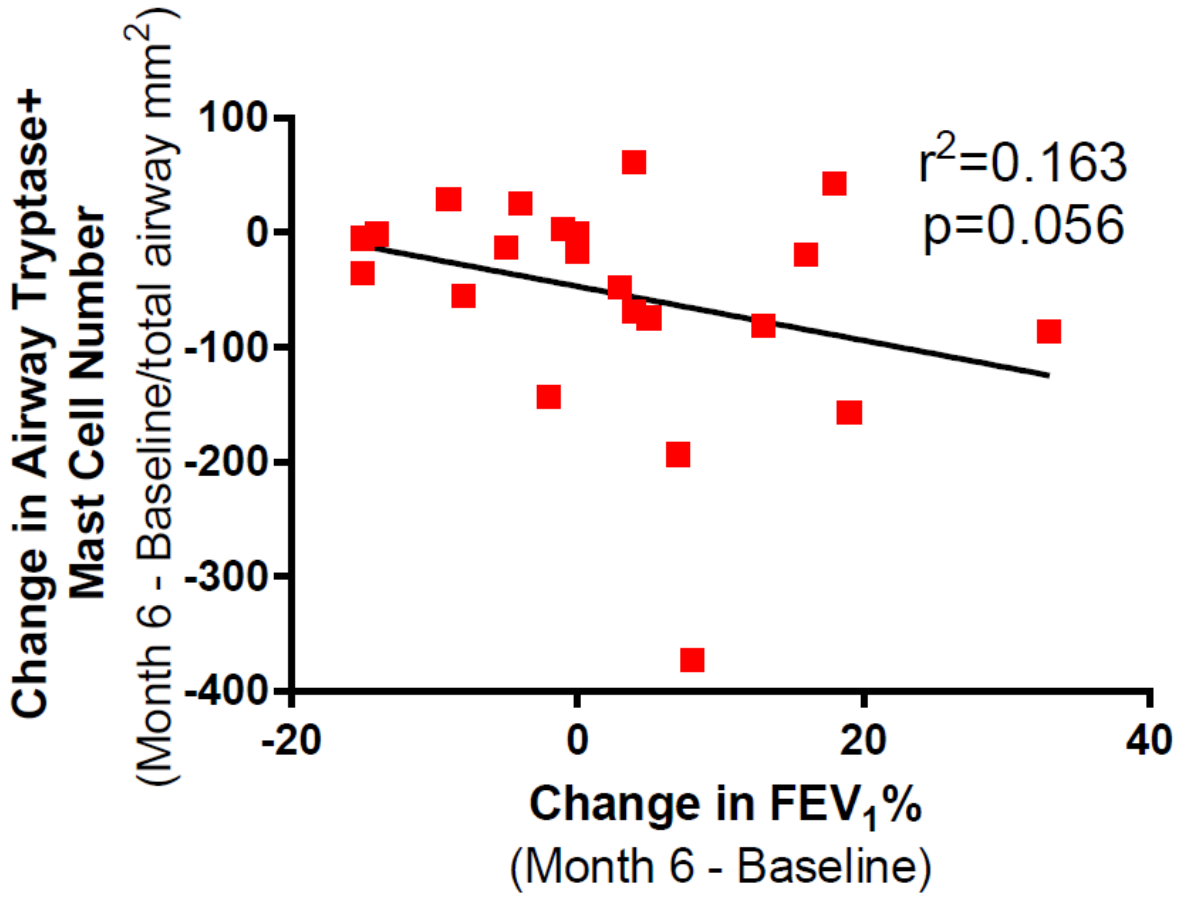
Supplemental Figure S1: Modeled Effect of Imatinib and Placebo on FEV_1 Over 24 Weeks.



Supplemental Figure 1. Modeled Effect of Imatinib and Placebo on FEV_1 Over 24 Weeks.

Shown are the modeled group mean FEV_1 at baseline, weeks 1, 2, 3, 4, 8, 12, 16, 20, 23, and 24.The p-value is 0.04 for the between-group difference in the change from baseline as assessed by the mixed model.

Supplemental Figure S2: Change in FEV_1% and Association with Airway Mast Cell Number

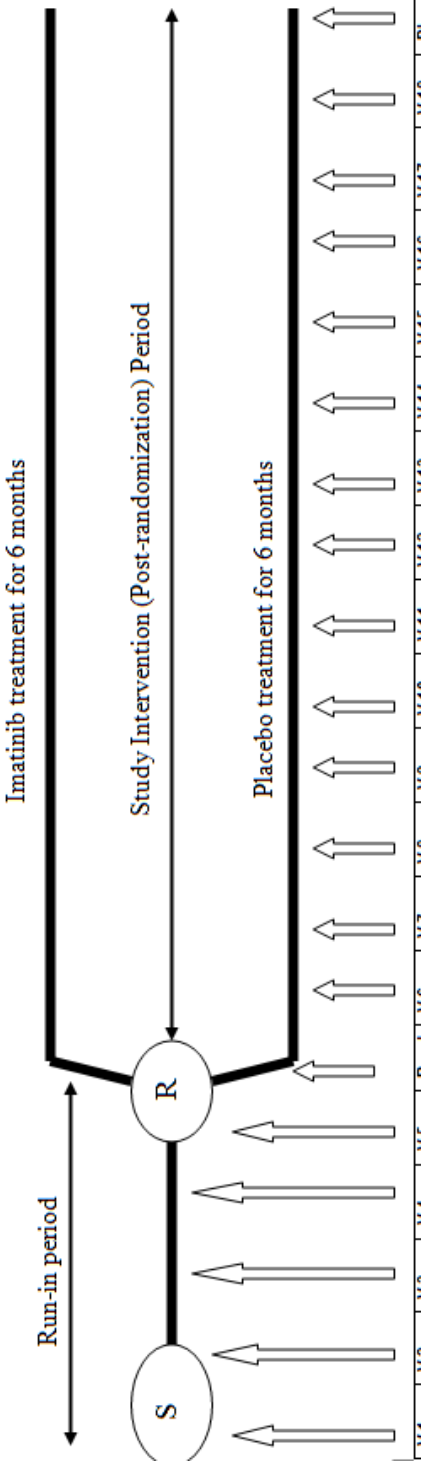


Supplemental Figure S2: Change in FEV_1% and Association with Airway Mast Cell Number

Shown is the Spearman rank correlation between the change in FEV_1% of predicted before the study to the end of the study and the change in total airway mast cell number as enumerated in endobronchial biopsies before treatment and at the end of treatment.

Supplemental Tables:

Supplemental Table S1. Detailed Study Procedure Schema



V1 –7 wk	V2 –5 wk	V3 –4 wk	V4 -3 wk	V5 -17 d	Rand 0 day	V6 Wk 1	V7 Wk 2	V8 Wk 3	V9 Wk 4	V10 Wk 8	V11 Wk 12	V12 Wk 13	V13 Wk 16	V14 Wk 20	V15 Wk 22	V16 Wk 23	V17 Day166	V18 Wk 24	Phone Wk 25
IC	Mr	Mr	4a	Mr		Mr	Mr	Mr	Mr	Mr	Mr	Mr	Mr	Mr	Mr	Mr	17a	Mr	Qu
Hist	Dr	Dr	Sp	Dr		Dr	Dr	Dr	Dr	Dr	Dr	Dr	Dr	Dr	Dr	Dr	Sp	Dr	
Qu	ACQ	ACQ	Max	Vs		ACQ	ACQ	ACQ	ACQ	ACQ	Qu	Vs	ACQ	ACQ	Vs	Vs	Max	Vs	
PE	Vs	Vs	CT	PBC		PE	PE	PE	PE	PE	PE	U	PE	PE	Pg	Pg	CT	PBC	
EKG	Pg	Pg		CRE		Sp	Sp	Sp	Labs	Labs	Labs	Pg	Labs	Labs	PK	Sp	17b	CRE	
Labs	Sp	Sp	4b-2d	U		Labs	Labs	Labs	EKG	EKG	Bl	Sp	EKG	EKG	Sp	Mch	Mr	Sp	
Sp	Mch	HSC	Mr	Sp		EKG	EKG	EKG	Pg	Pg	PK	Mch	Pg	Pg	HSC	Dd	Dr	Bron	
Dd	Dd	Skin	Dr	Bron		Dd	Dd	Dd	NO	NO	EKG	Dd	NO	NO	Dd		Qu		
		Dd	Qu	Md			Md		Sp	Sp	Pg		Sp	Sp			PPP		
			PE	Dd					Md	Max	NO		Md	Md			Bl		
			Bl						Dd	Md	Sp		Dd	Dd			Labs		
			PPP							Dd	Skin						U		
			EKG								HSC						EKG		
			Pg								Md						PE		
			NO								Dd						Pg		
			EBC														NO		
			Sp														EBC		
			Sput														Sp		
			Dd														Sput		
																	Skin		
																	Dd		

Abbreviations used: **Bl**: Blood for (IL-9R-alpha+ CD34/c-Kit/CD13+ peripheral blood cells including mast cells, **IgE**, Future Genotyping, Blood for GWAS; **Bron**- bronchoscopy procedure; **CRE** – Cardio-respiratory exam, **CT**-CT scan chest; **Dd**- diary dispensation; **Dr**- Diary review; **EBC**-exhaled breath condensate; **Hist**- history; **HSC**- hypertonic saline challenge; **IC**- informed consent; **Lab**- Safety Labs (WBC with differential, Hematocrit, Platelet count, CMP including eGFR, LFTs);**Max**- maximum bronchodilator reversibility; **Mch**- mathacholine challenge test; **Md**- medication dispensation; **Mr**- Medication review; **NO**-eNO measurement; **PBC**- Pre-Bronch Checklist; **PE**- physical exam; **Pg**- pregnancy test; **PK**- pk monitoring; PPP – PT,PTT and Platelets count, **Qu**- questionnaires (ACQ, AQLQ, ASUI, SFDQ); **R**- Randomization; **S**- Screening; **Skin**- allergy skin test; **Sp**- spirometry; **Sput**- sputum induction and processing; **U**- Urine collection (PGD2 metabolite, 9α-11β-PGF2) ; **Vs**- Vital signs

Visits Window Period: V-2, 3,4a, 6, 7, 8, 9, 13, 15, 16 and 17a can be scheduled within ± 3 days of window period. V-10, 11, 13 and 14 can be scheduled within a window period of 5 days. Randomization will be performed 7-14 days after the bronchoscopy procedure (V-5). Bronchoscopy should be performed within 4 days of the V-4 Bl, NO, EBC and Sput. Deviations will require protocol exceptions.

Supplemental Table S2. Adverse Events.

	Placebo n (% of participants) [#]	Imatinib n (% of participants) [#]	P-value
Total Adverse Events Reported*	118(80)	123(94)	0.86
Severe Adverse Events*	5(16.7)	3(9.4)	0.53
Serious Adverse Events	6(18.8)	2(6.7)	0.16
Allergy/Immunology	6(20)	3(9)	0.18
Auditory/Ear	0(0)	1(3)	1
Blood/Bone Marrow	2(7)	5(16)	0.43
Leukopenia	0(0)	2(6)	0.49
Anemia	0(0)	1(3)	1
Cardiac	1(3)	0(0)	1
Constitutional	3(10)	1(3)	0.35
Dermatologic	7(23)	10(22)	0.55
Gastrointestinal *	9(20)	17(31)	0.17
Nausea	2(7)	6(19)	0.26
Diarrhea	3(10)	6(19)	0.48
Hemorrhage/Bleeding	1(3)	0(0)	0.48
Infection *	30(53)	21(60)	0.14
Lymphatics	1(3)	1(3)	1
Metabolic/Laboratory*	2(7)	14(34)	0.013
Hypophosphatemia	0(0)	6(19)	0.02
Hypokalemia	0(0)	3(9)	0.24
Elevated Aspartate Aminotransferase	0(0)	3(9)	0.24
Musculoskeletal/Soft Tissue *	8(23)	15(31)	0.20
Muscle cramps (leg, foot) *	2(7)	10(19)	0.046
Neurologic/Psychiatric*	5(10)	4(9)	0.67
Pain*	13(30)	3(9)	0.017
Respiratory *	25	24	0.71
Asthma Exacerbations*	20(47)	16(41)	0.36
Renal/GU	0(0)	1(3)	1
Surgery	3(10)	2(6)	0.67

*****Poisson regression model was used. [#]Number and percent of participants in each group who reported each type of adverse event. All events that occurred after randomization were included. n denotes number of participants reporting each type of adverse event.

Supplemental Table S3: Severe Adverse Events

GROUP	PARTICIPANT	ADVERSE EVENT	Related to Drug	Related to Protocol	Serious
Imatinib	1	Asthma Exacerbation	Possible	Not related	Yes
	1	Asthma Exacerbation	Not related	Probable	Yes
	1	Anaphylactic Reaction	Not related	Not related	Yes
	2	Nausea post-bronchoscopy	Definite	Possible	Yes
	2	Leukocytosis post-bronchoscopy	Definite	Possible	Yes
	3	Bilateral Leg Cramps	Probable	Probable	No
	3	Hypokalemia	Probable	Probable	No
Placebo	1	Asthma Exacerbation	Not related	Not related	Yes
	1	Asthma Exacerbation	Not related	Not related	Yes
	2	Asthma Exacerbation	Possible	Not related	Yes
	2	Asthma Exacerbation	Possible	Not related	Yes
	2	Acute Upper Respiratory Tract Infection	Possible	Not related	Yes
	3	Asthma Exacerbation	Not related	Not related	Yes
	3	Asthma Exacerbation	Not related	Not related	Yes
	4	Ankle Dislocation	Not related	Not related	Yes
	5	Angioedema	Not related	Not related	No

Supplemental Table S4: Baseline values for outcome measures

Baseline Parameter – mean ± SD	Imatinib	Placebo
Serum Tryptase (ng/mL)	4.96±2.25	4.70±2.04
BAL Fluid Tryptase (ng/mL)	1.34±2.19	0.96±0.91
Total Airway Tryptase+ MCs (/mm^2)	129.6±91.7	146.2±85.9
Airway Smooth Muscle Tryptase+ MCs (/mm^2)	174.4±174.6	208.2±190.0
BAL PGD_2 (pg/mL)	33.0±51.4	37.7±51.0
BAL cysLTs (pg/mL)	55.3±34.3	56.8±22.2
BAL Histamine (nM)	0.92±1.01	2.70±12.22
BAL Tryptase (ng/mL)	1.64±2.70	0.91±0.90
Urinary PGD-M (ng/mg Cr)*	2.82±1.7	1.87±0.99
Urinary LTE_4 (ng/mg Cr)	0.15±0.23	0.11±0.16
BAL Eosinophil %	0.95±1.43	3.0±10.98
Airway Wall Thickness (%)	0.306±0.042	0.325±0.038
Airway Wall Area (%)	0.62±0.04	0.64±0.03

SD denotes standard deviation, MC mast cell, BAL bronchoalveolar lavage, PGD_2 prostaglandin D_2, cysLTs cysteinyl leukotrienes, PGD-M prostaglandin D_2 metabolite, and LTE_4 leukotriene E_4. * p=0.04.

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