An updated model for prediction of asthma exacerbations using albuterol electronic multi-dose dry powder inhaler

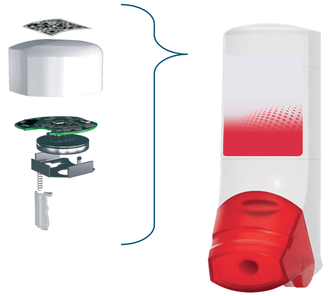
Rajan Merchant,[1] Guilherme Safioti,[2] Lena Granovsky,[3] Michael Reich,[3] Thomas Li,[4] Tanisha Hill,[4] Randall Brown,[4] Roy Pleasants,[5] Giselle Mosnaim,[6] Michael DePietro[4]

[1]Woodland Clinic Medical Group, Allergy Department, Dignity Health, Woodland, CA, USA; [2]Teva Pharmaceutical Industries Ltd, Amsterdam, Netherlands; [3]Teva Pharmaceutical Industries Ltd, Petah Tikva, Israel; [4]Teva Branded Pharmaceutical Products R&D Inc., West Chester, PA, USA; [5]Division of Pulmonary Medicine and Critical Care, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC, USA; [6]NorthShore University HealthSystem, Evanston, IL, USA

Background

- Early detection of impending asthma exacerbations would provide opportunities for pre-emptive treatment and improve asthma action plans.[1,2] Previous predictive models for asthma exacerbations have had a limited accuracy for imminent events.[3,4]
- A predictive model for impending exacerbations was successfully developed using data gathered from the ProAir® Digihaler™ (albuterol 90 µg/dose; **Figure 1**), an electronic multi-dose dry powder inhaler (eMDPI) with integrated sensors.[5,6]
- Using additional patient information and baseline data, the initial model was refined to improve the predictive accuracy.

Figure 1 ProAir Digihaler



Methods

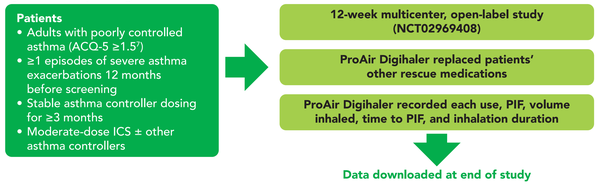
Study design

- The predictive model was developed using data from a 12-week, open label study (NCT02969408), conducted between February 2017 and February 2018.
- Digihaler passively recorded time and date of albuterol use and inhalation parameters: peak inspiratory flow (PIF), time to PIF, inhalation volume, and inhalation duration.
- Data were downloaded from inhalers and analyzed at the end of the study (**Figure 2**).
- An exacerbation was defined as an event where the patient was required to increase their dose of oral corticosteroids and attended an unscheduled provider visit (e.g. urgent care visit, hospitalization).

Machine learning modelling

- Case report form (CRF) data, such as medical history, body mass index (BMI), and blood pressure, were combined with Digihaler data and subjected to a machine learning algorithm to refine a model predictive of impending exacerbations.

Figure 2 Study design



ACQ-5, Asthma Control Questionnaire-5; ICS, inhaled corticosteroids; PIF, peak inspiratory flow.

- Algorithms were trained on patient-specific inhalation information collected from Digihalers, as well as age, BMI, blood pressure, and the number of exacerbations and hospitalizations in past 12 months
  - Baseline features and features prior to prediction, comparison between the two, and trends of changes in these features were subjected to supervised machine learning algorithms
  - A 4-fold cross validation technique was used to compare performance metrics and gradient boosting trees were chosen as the best algorithm. The generated model was evaluated by receiver operating characteristic area under curve (ROC AUC) analysis.

Results

- A total of 360 patients completed the study with ≥1 valid inhalation from Digihaler and were included in the analysis; of these, 64 patients experienced a total of 78 exacerbations.
- Demographics and inhalation characteristics for patients enrolled in the study are shown in **Table 1**.

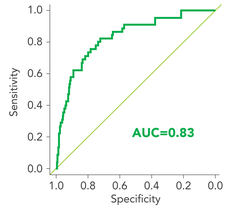
Table 1 Demographics and inhalation characteristics

	Full study period		10 days prior to an exacerbation
	Patients without exacerbation(s), (n=296)	Patients with exacerbation(s), (n=64)	Patients with exacerbation(s), (n=64)
Mean age, years (range)	49.5 (18.0–82.0)	52.0 (25.0–87.0)	52.0 (25.0–87.0)
Females, n (%)	235 (79.4)	55 (85.9)	55 (85.9)
Mean PIF, L/min (SD)	73.18 (20.3)	73.37 (23.1)	71.78 (23.2)
Mean inhalation volume, L (SD)	1.45 (0.75)	1.44 (0.70)	1.44 (0.77)
Mean inhalation duration, seconds (SD)	1.62 (0.88)	1.60 (0.79)	1.61 (0.83)
Mean time to PIF, seconds (SD)	0.55 (0.41)	0.56 (0.43)	0.58 (0.46)

PIF, peak inspiratory flow; SD, standard deviation.

- The refined predictive model improved the ability to predict an impending exacerbation 5 days in advance with an ROC AUC of 0.83 (sensitivity 68.8%, specificity 89.1%; **Figure 3**).

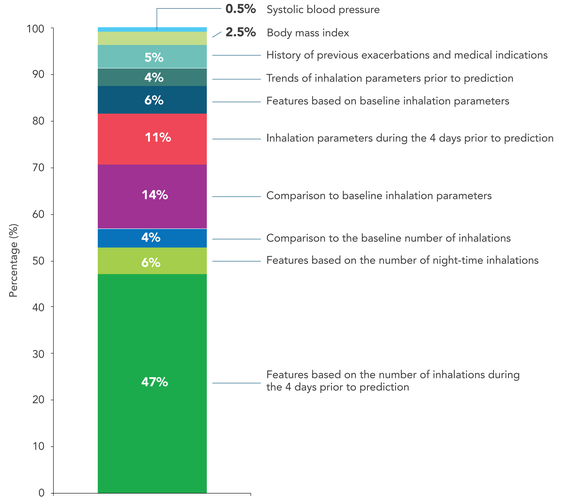
Figure 3 ROC curve for updated model predicting exacerbations within the following 5 days



AUC, area under curve; ROC, receiver operating characteristic.

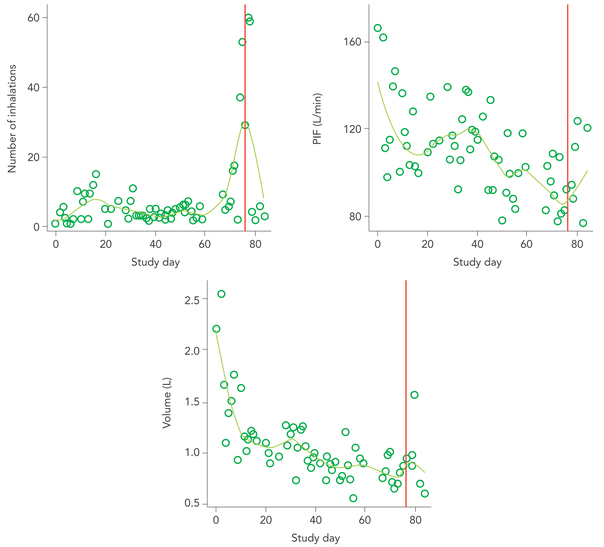
- The most significant factors contributing to the refined model are shown in **Figure 4**.

Figure 4 The most significant features of the predictive model



- A patient example showing the number of inhalations, inhalation volume and PIF by study day and prior to an exacerbation can be seen in **Figure 5**
  - It should be noted that not all patients show this pattern.

Figure 5 Inhalations, inhalation volume and PIF of a patient during the study



The red vertical line represents a confirmed asthma exacerbation. PIF, peak inspiratory flow.

Conclusions

- Digihaler data, including the inhalation characteristics, in combination with CRF information, resulted in an improvement of the 5-day exacerbation predictive model ROC AUC to 0.83.
- Additional studies, and potentially the inclusion of other data sources, will further refine the model and increase its predictive value.
- Real-life monitoring data collected via eMDPIs, such as the ProAir Digihaler, could help improve asthma management and enable pre-emptive interventions to minimize exacerbations, improve quality of care and reduce healthcare costs.

Presented at: AAAAI 2020, Philadelphia, Pennsylvania, USA; March, 13–16 2020

Disclosures: RM reports a one-time honorarium from Propeller Health for his participation in an advisory board meeting. RP has received grants from Boehringer Ingelheim and personal fees from Grifols, Sunovion, and Teva Pharmaceuticals. GM has received research grant support from AstraZeneca and GSK and currently receives research grant support from Propeller Health; owned stock in electroCore; and served as a consultant and/or member of a scientific advisory board for GSK, Sanofi/Regeneron, Teva, Novartis, AstraZeneca, Boehringer Ingelheim and Propeller Health. GS, LG, MR, TL, TH, RB, and MD are employees of Teva Pharmaceuticals.

Acknowledgments: Medical writing support was provided by Melanie Francis, of Zoetic Science (an Ashfield company, part of UDG Healthcare plc), and was funded by Teva Branded Pharmaceutical Products R&D Inc.

Role of the funding source: Funding was provided by Teva Branded Pharmaceutical Products R&D Inc. Teva employees were involved in the study design, data collection and analysis, and in the writing of this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References: 1. Bateman ED, et al. J Allergy Clin Immunol 2015;135:1457–64; 2. Spyroglou II, et al. BMC Res Notes 2018;11:522; 3. Finkelstein J, Jeong IC. Ann N Y Acad Sci 2017;1387:153–65; 4. Messinger AI, et al. Am J Respir Crit Care Med 2018;198:291–304; 5. ProAir Digihaler. Available at: https://www.proairdigihaler.com; 6. Safioti G, et al. American Thoracic Society Conference, Dallas, TX, USA, 17–22 May 2019; poster 693; 7. Korn S, et al. Ann Allergy Asthma Immunol. 2011;107:474–9.