Study Protocol

EffectIveness of bioloGics (by classes) in patieNts with dIfferent combinations of T2 biomarkErs (IGNITE)

An investigation into biomarker information needed to make informed predictions of patient responsiveness to biologic treatment by biologic class

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TITLE	**EffectIveness of bioloGics (by classes) in patieNts with dIfferent combination of T2 biomarkEr s (IGNITE)**
Subtitle	An investigation into biomarker information needed to make informed predictions of patient responsiveness to biologic treatment according to biologic class
Protocol version number	V1.0
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Study aims and objectives	**Study aims:** To investigate whether T2 inflammatory biomarker measurements tend to be correlated within patients, and whether biomarker traits are associated with responsiveness to treatment with biologics **Study objectives:** **Objective 1**: To describe distributions of T2 inflammatory biomarkers in severe asthma patients, and examine whether different T2 biomarker measurements are correlated within patients **Objective 2**: To examine whether T2 biomarker measurements are associated with responsiveness to treatment with biologics **Objective 3:** To identify whether multiple biomarker measurements lead to better prediction of patient responsiveness to biologics
Countries of study	Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Korea, Kuwait, Mexico, Portugal, Saudi Arabia, Spain, Taiwan, United Arab Emirates (UAE), United Kingdom (UK), United States of America (USA)
Author(s)	Sarah Burkill

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADEPT	Anonymised Data Ethics & Protocol Transparency
ANOVA	Analysis of variance
BEC	Blood eosinophil count
BMI	Body mass index
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
GEE	Generalised estimating equation
GINA	Global Initiative for Asthma
IgE	Immunoglobulin E
ICS	Inhaled corticosteroids
IL-4, -5, -13	Interleukin-4, -5, -13
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
R	R software from the R Project for Statistical Computing
STATA	Stata software suite
T2	Type 2 inflammation

1.0 Background

Severe asthma can be defined as asthma which remains uncontrolled, or which requires extensive treatment according to steps 4 and 5 of the Global Initiative for Asthma (GINA)[1], with recent estimates indicating 6.1% of asthma patients could fall into this category[2]. Biomarkers, defined as objectively measured characteristics which indicate biological processes[3], are increasingly used as indicators of disease presentation in many areas of medicine. Treatment of severe asthma is often determined based on biomarker measurements including blood eosinophil count (BEC), IgE measurements, and fractional exhaled nitric oxide (FeNO)[4]. This can be limiting if measurements are only considered as individual observations, rather than being taken in the context of other information including other biomarker values[4]. Additionally, biomarker measurements are often placed in a binary classification according to whether high levels of T2 inflammation are present or not, although where cut offs should be drawn is still debated[5,6]. Using binary cut offs in this way means information is lost, making it more difficult to tailor treatments to patients. Biomarker values are becoming increasingly important in understanding asthma endotype and treatment responsiveness[7], so it is crucial the right and most useful information is collected. Understanding whether using precise measurements rather than considering information only in terms of binary cut offs improves predictions of how well patients tend to respond to treatment appears to be an understudied area. Studying exactly what information is needed, and at what level of granularity, would therefore provide useful information for asthma clinicians when deciding what data needs to be collected from patients at each visit.

More recent asthma research has made a distinction between asthma control and asthma severity[8], with good asthma control being the intention of treatment. Asthma control refers to the extent to which presentations of asthma can be reduced or removed by therapy. In order to understand how well treatment works for individual patients, change in exacerbation rates before and after treatment initiation is often more insightful than simply considering exacerbation levels over the course of treatment exposure[9]. Exacerbations can have many causes, with susceptibility dictated by factors such as allergic sensitisation, genetic variation, and defective anti-viral immunity[10,11]. Comorbid diseases can also act as exacerbation triggers[12–14]. Knowledge on whether these exacerbation triggers can be identified prior to an exacerbation occurring through biomarker values would mean clinicians may be able to predict if an exacerbation is likely to occur and respond accordingly, improving overall asthma control for patients[11].

Asthma patients are a heterogenous group, and asthma patients with similar severity could present differently in terms of their biomarker measurements and responsiveness to treatments[15,16]. Severe asthma patients are thought to constitute 6.1% of all asthma patients when the GINA definition is used[2], however they are estimated to account for half of asthma healthcare-related costs[17]. Therefore, understanding how these patients respond best to treatment and how exacerbations can be reduced is of optimum importance. Differences in biomarker measurements between patients may assist with prediction of how well treatments are likely to perform, however, full information is not always collected or available for each patient. Understanding what information is needed in order to make more precise predictions as to patient responsiveness to treatment would provide useful insight into how much data should be collected on each patient during visits. Knowledge of specific patient presentation and phenotype through use of biomarkers can assist with making decisions on the most appropriate treatment regimens. We propose an investigation into which measurements should be taken when patients visit their clinicians, to generate useful predictions of how well patients are likely to respond to treatment.

2.0 Study Aims and Objectives

2.1 Study Aims

To investigate whether T2 inflammatory biomarker measurements tend to be correlated within patients, and whether biomarker traits are associated with responsiveness to treatment with biologics

2.2 Study Objectives

Objective 1: To describe distributions of T2 inflammatory biomarkers in severe asthma patients, and examine whether different T2 biomarker measurements are correlated within patients

Objective 2: To examine whether T2 biomarker measurements are associated with responsiveness to treatment with biologics

Objective 3: To identify whether multiple biomarker measurements lead to better prediction of patient responsiveness to biologics

3.0 Study Design

This study aims to consider firstly whether biomarker measurements tend to be correlated, and secondly whether knowledge on multiple biomarkers can improve prediction of how well patients respond to biologics treatment. This will be done stratified by biologics class. The specific study design will depend on which is the most appropriate for each objective.

Objective 1: This objective will be observational and **cross sectional**, considering highest biomarker measurement across visits. Distributions for biomarkers, and whether associations exist between different biomarkers within patients, will be the focus. This will include considering distributions and correlations both in the context of biomarkers as continuous variables, and as variables which use cut offs to define high and low T2 inflammatory involvement in order to assess whether measurement granularity is important.

Objective 2: This objective will be studied through a **longitudinal observational** approach and will consider changes to number of exacerbations in the year preceding treatment initiation, with number of exacerbations in the year following treatment initiation. The analysis will consider whether number of exacerbations appears to reduce more for those with evidence of high T2 inflammatory biomarkers for at least one biomarker, relative to those with lower levels of T2 inflammatory involvement in their asthma presentation prior to treatment initiation. This study will stratify by biologics class. Whether there are changes to pre-treatment lung function and asthma control, relative to lung function and asthma control at 24 weeks to 1 year post treatment initiation will also be assessed.

Objective 3: This objective will take a **longitudinal observational** approach and is focused on whether information on one biomarker is sufficient for predicting patient responsiveness to treatment with biologics, or whether there should be knowledge on several biomarkers for adequate predictions to be made. If knowledge on one biomarker is shown to be sufficient, this would be beneficial for prescribing clinicians when considering what information needs to be collected from patients at each visit to inform treatment options. Analysis will use biologic naïve patients only.

4.0 Study Population

4.1 Data Sources

The International Severe Asthma Registry (ISAR) is an international collaborative initiative aiming to gather longitudinal data on severe asthma patients. Those eligible for enrolment are patients aged 18 or over visiting a participating centre. They must have been diagnosed with severe asthma and provided informed consent for their data to be collected. Severe asthma is defined as asthma which is uncontrolled despite treatment, or which requires extensive treatment as outlined by steps 4 and 5 of GINA[1].

Data collection began in 2018, and as of July 2021, there were **11,439** participants from 24 countries enrolled into ISAR. Of these enrolled participants, **8,728** were prospective level patients[18]. There are currently **3938** (preliminary number) patients with data available on all three biomarkers (Blood Eosinophil Count (BEC), Fractional exhaled Nitric Oxide (FeNO), and Serum immunoglobulin E (IgE)). The data is comprised of relevant information collected from patients at each visit, and extracted medical records.

4.2 Inclusion and Exclusion Criteria

Inclusion Criteria:

Objective 1:

- All patients with available biomarker information

Objective 2:

- All patients with relevant biomarker, biologics treatment, and exacerbation, lung function and asthma control information

Objective 3:

- All patients with relevant biomarker, biologics treatment, and outcomes information

Exclusion Criteria:

Objectives 1, 2, and 3 :

None

5.0 Study Variables

The following variables will be used to derive an analysis dataset suitable for the objectives of the study. Whether the variables are part of the core ISAR database, or whether they are part of the bolt-on datasets is also indicated in the variable list. Bolt-on data is available for approximately half of ISAR participants as of July 2021 and applies to co-morbidity variables for this study.

5.1 Patient Identifier and Demographic Variables

Label	Type	Values	Core	Optional
Identifying patients				
Patient identifiers	String	String	✓	
Identifying visits				
Visit identifiers for each patient	String	String	✓	
Demographic and background variables				
Gender	Binary	Male, Female, Missing	✓	
Ethnicity	Categorical	Caucasian, Southeast Asian, Northeast Asian, African, Mixed, Other, Unknown	✓	
Country from which patient was recruited	String	Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Korea, Kuwait, Mexico, Portugal, Saudi Arabia, Spain, Taiwan, UAE, UK, USA	✓	
Age at asthma onset	Numeric	Numeric value	✓	
Age at study entry	Numeric	Numeric value	✓	
Body mass index (BMI)	Numeric	Numeric value	✓	
Smoking status	Categorical	Current smoker, ex-smoker, never smoked	✓	

5.2 Biomarker Variables

Label	Type	Values	Core	Optional
Biomarkers for defining phenotype				
When IgE was measured	String	Date variable	✓	
Highest recorded IgE levels	Numeric	Numeric value	✓	
Were FeNO levels taken in the past year	Binary	Yes, No, Missing	✓	
When FeNO levels were taken	String	Date variable	✓	
Highest recorded FeNO levels	Numeric	Numeric value	✓	
When BEC was measured	String	Date variable	✓	
Highest recorded BEC	Numeric	Numeric value	✓	
Whether any FeNO levels were taken prior to treatment initiation	Binary	Yes, No, Missing	✓	
Whether any BEC levels were taken prior to treatment initiation	Binary	Yes, No, Missing	✓	
Whether any IgE levels were measured prior to treatment initiation	Binary	Yes, No, Missing	✓	
IgE reading at each visit	Numeric	Numeric value	✓	
BEC reading at each visit	Numeric	Numeric value	✓	
FeNO reading at each visit	Numeric	Numeric value	✓	

5.3 Defining Treatment

Label	Type	Values	Core	Optional
Defining treatments				
When treatment was prescribed	String	Date variable	✓	
Was treatment a biologic	Binary	Yes, No	✓	
Was treatment an oral corticosteroid (OCS)	Binary	Yes, No	✓	
Specific treatment name	Categorical	OCS, ICS, ICS/LABA, LABA, LAMA, theophylline, LTRA, anti-IgE, anti-IL5, anti-IL4, macrolide, steroid sparing, LABA/LAMA	✓	
When treatment ended	String	Date variable	✓	

5.4 Defining Treatment Responsiveness

Label	Type	Values	Core	Optional
Defining treatment responsiveness				
Number of exacerbations in year preceding treatment initiation	Numeric	Numeric value	✓	
Number of exacerbations in year following treatment initiation	Numeric	Numeric value	✓	
When exacerbation occurred	String	Date variable	✓	

Lung function at treatment initiation	Numeric	Numeric value	✓
Lung function 24 weeks/1 year after treatment initiation	Numeric	Numeric value	✓
Highest lung function measure	Numeric	Numeric value	✓
Date lung function measured	Numeric	Date variable	✓
Were FeNO levels taken in the past year	Binary	Yes, No	✓
When FeNO levels were taken	String	Date variable	✓
FeNO levels	Numeric	Numeric value	✓
Asthma control at baseline	Categorical	Well controlled, Partially controlled, Not controlled	✓
Asthma control 24 weeks/1 year after treatment initiation	Categorical	Well controlled, Partially controlled, Not controlled	✓
Type of rescue steroid used during exacerbation	Categorical	Betamethasone, Deflazacort, Dexamethasone, Hydrocortisone, Prednisone, Prednisolone, Methylprednisolone, Triamcinolone acetonide, Other	✓
Date rescue steroid initiated	String	Date variable	✓
Date rescue steroid stopped	String	Date variable	✓
Dose of rescue steroid prescribed	String	Dosing value	✓
Frequency per day of prescribed rescue steroid use	String	Daily frequency value	✓

5.5 Comorbidities

Label	Type	Values	Core	Optional
Comorbidity				
Obstructive sleep apnoea	Binary	Yes, No		✓
Rhinitis	Binary	Yes, No	✓	
Nasal polyposis	Binary	Yes, No		✓
Aspergillosis	Binary	Yes, No		✓
Anxiety	Binary	Yes, No		✓
Depression	Binary	Yes, No		✓
Cardiovascular disease	Binary	Yes, No		✓
Metabolic disease	Binary	Yes, No		✓
Positive allergy test	Binary	Yes, No	✓	
Other allergies	Binary	Yes, No	✓	
Type of allergy	Categorical	Dust Mite, Grass mix, Cat hair, Mould mix, Dog hair, Aspergillus, Weed Mix, Trees, Food mix, Animal Mix, Other	✓	
Osteoperosis	Binary	Yes, No		✓
Heart failure	Binary	Yes, No		✓
Myocardial infarction	Binary	Yes, No		✓
Stroke	Binary	Yes, No		✓
Glaucoma	Binary	Yes, No		✓
Cataract	Binary	Yes, No		✓
Renal failure	Binary	Yes, No		✓
Peptic ulcer	Binary	Yes, No		✓
Gastroesophogeal reflux disease	Binary	Yes, No		✓
COPD	Binary	Yes, No		✓

ABPA	Binary	Yes, No	✓
Dysfunctional breathing	Binary	Yes, No	✓
Pneumonia	Binary	Yes, No	✓
Pulmonary embolism	Binary	Yes, No	✓
Osteoperosis	Binary	Yes, No	✓
Type 2 diabetes	Binary	Yes, No	✓
EGPA	Binary	Yes, No	✓
Hypertension	Binary	Yes, No	✓

5.6 Hospital Admissions

Label	Type	Values	Core	Optional
Identifying hospital admissions				
Number of hospital visits in the past year	Numeric	Numeric value	✓	
Number of hospital admissions in the past year	Numeric	Numeric value	✓	

6.0 Study Outcomes

The outcomes for each study will be determined by the objectives being addressed.

6.1 Objective 1:

This objective will be focused on determining whether biomarker measurements tend to be associated (i.e., does a measurement indicating high T2 inflammatory involvement for one measure tend to mean high T2 measures for other biomarkers). Therefore, the outcomes will be highest biomarker measurements for each patient. For the purposes of assessing whether granularity of the measurement is important, each highest measurement will also be recoded to binary stating whether the measurement indicates high T2 inflammatory involvement or not. A sensitivity analysis will also be undertaken which takes into consideration the potential effects of treatment on biomarker values (see sensitivity analysis description on pages 17-18 for more details).

6.2 Objective 2:

The second objective looks at treatment responsiveness according to biomarker levels, and biologics class. Outcomes for exacerbations will therefore be number of exacerbations in the year preceding treatment initiation, number of exacerbations in the year following treatment initiation, and most importantly the difference in these numbers to assess whether treatment appears to have effectively reduced exacerbations for each patient. Additionally, lung function and asthma control at treatment initiation will be compared to lung function and asthma control at 24 weeks to 1 year after treatment initiation. This will give insight into the extent to which exacerbation levels drop, and whether lung function and asthma control improve, and therefore whether there are certain patient groups which seem to respond particularly well to biologics treatment initiation.

6.3 Objective 3:

This objective is focused on determining exactly how much biomarker information is needed to make reasonably accurate predictions of patient responsiveness to treatment. Therefore, the outcomes will relate to key asthma outcomes including lung function, extent of asthma control, and exacerbations. The number of biomarkers needed to make accurate predictions of these outcomes will be assessed through model fit, and whether there are substantial changes in estimates of probability of the outcome occurring when additional biomarkers are considered.

7.0 Statistical Analysis

7.1 Sample Size

The final sample size will depend on the number of individuals with available biomarker, treatment, exacerbation, lung function, and asthma control data.

7.2 Software

Analysis will be undertaken in STATA and R. Datasets will be received from the data analytics team in CSV, which can be easily imported into both STATA and R.

7.3 Analysis

Objective 1: This objective will describe biomarker distributions for patients, and test associations between biomarker values across patients, using linear and logistic regression depending on the format of the variable. This will give insight into whether having a high biomarker value for one measurement is associated with having a high value for at least one other biomarker. These associations will be tested using both the continuous values for each biomarker (linear regression), and the binary recoding which indicates whether the patient has evidence of high levels of T2 inflammatory involvement according to each measurement (logistic regression). Given that it is still debated as to where cut offs should be drawn to define high T2 inflammation, we may use several definitions in different sensitivity analyses.

For this objective, we aim to conduct a **sensitivity analysis** which takes into account the potential effect of treatment on biomarker values.

Table 1 shows the extent to which each biomarker is thought to respond to particular treatments, and therefore how the final sensitivity analysis criteria was arrived at.

Table 1:

	BEC	**IgE**	**FeNO**
Anti-IL4/13	No change	No change	Reduced ↓↓↓
Anti-IL5	Reduced ↓↓↓	No change	Reduced
Anti-IgE	Reduced ↓	Slight increase	Reduced ↓↓

We aim to investigate whether biomarker measurements are associated based on an individuals' 'natural' level of inflammation. Therefore, for all treatments which reduce

biomarker measurements, the sensitivity analysis will exclude patients on these treatments if they do not have any measurements taken prior to treatment initiation, as their highest measurement is likely to be taken at a time when their T2 inflammation is suppressed. For all treatments which increase biomarker values, the highest value prior to treatment initiation will be the value used in the analysis. If there are no measurements prior to treatment initiation, these patients will be excluded.

Objective 2: Firstly, data will be described and associations tested through t-tests or ANOVA, or chi-square depending on the format of the variable. Change in exacerbations will be of primary interest. Generalised estimating equations (GEEs) will then be used, which can take into account within person clustering, to assess changes to the number of exacerbations in the year prior to treatment initiation, relative to number of exacerbations in the year following treatment initiation using biologics. This analysis will be categorised according to whether patients measure high for one, or more, of their biomarkers for T2 inflammation, prior to treatment initiation. This will give insight into how patients respond according to whether their T2 inflammatory biomarkers are considered to be high or not. As with objective 1, different cut offs for defining high T2 may be used in different sensitivity analyses given that where such cut points should be made is still debated. In addition, analysis will be stratified according to biologics class to assess whether there are differences in treatment responsiveness, or differences between groups with high or low T2 inflammation according to biologic class. The same approach will be used to compare lung function and degree of asthma control at biologics initiation, to lung function and asthma control after 24 weeks to 1 year after treatment start.

Objective 3: Data will be described, and tests of association conducted where relevant. Negative binomial regression will be used to assess whether there are changes in rates of exacerbation over time. Ordinal regression will be used to assess asthma control, and linear regression will be used to assess lung function. Backward stepwise models will assist in deciding whether the addition of more biomarker variables to the models for each outcome over the year following treatment initiation improves the fit of the model. This will allow us to draw conclusions on whether information on several biomarkers leads to better fitted models for predicting responsiveness to biologics, relative to the inclusion of fewer biomarkers.

8.0 Feasibility Assessment

For objective 1, we are somewhat limited when it comes to knowledge of a patient's highest biomarker measurements (or highest measurement prior to treatment initiation). This can only be the highest measurement that we have included in our data, and it will be the decision of each clinician as to whether such measures should be taken and when. This could result in some degree of selection bias, as it is possible clinicians only see a need for a measurement to be taken for particular patient groups. Whilst only patients with information on all three biomarkers will be included in the analysis for objectives 1 and 2, data will be described for all patients to consider whether there appear to be differences in those with 0, 1, 2, or 3 biomarker measurements taken. If it seems as though patients with information on all biomarkers are a specific subset of patients, results will not be generalisable to the whole severe asthma population. It may be insightful, if it appears selection bias is occurring, to run sensitivity analyses using patients with fewer biomarkers available to consider whether conclusions would have been the same. Additionally, some patients may have measurements recorded for some, but not all, of the biomarkers intended for use in this study, which reduces statistical power. However, data is available for all 3 biomarkers for **3,938 patients (preliminary number**), which we believe will still provide adequate power to address the research questions.

For objectives 2 and 3, it will only be possible to assess responsiveness to pharmacotherapy. How well patients respond to physical or psychological therapies cannot be assessed, given that this data is not collected as part of ISAR. Additionally, gaining a full, unbiased estimate of study time will be difficult for these objectives. This is because it is more likely the case that exact date of treatment initiation, and therefore information on time exposed to treatment, is available for biologics treatments relative to any non-biologics treatments. Therefore, full exposure time is available for some treatments, but not others. This study will, however, focus on biologics treatments, so analysis may be limited to only biologics patients for these objectives.

9.0 Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with ENCePP (www.encepp.eu).

ISAR is approved by the Health Research Authority for clinical research use, and governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee. We will submit the finalised version of this protocol to the ADEPT committee (https://www.regresearchnetwork.org/adept-committee/) for approval.

All sites will enter into a regulatory agreement in compliance with the specific data transfer laws and legislation pertaining to each country and its relevant ethical boards and organisations. Further, all data extracted to be transferred from sites will be hashed and will enter the research database in the form of anonymised patient IDs. The data will be retrieved by OPC data analysts and utilised as an anonymised dataset to perform the analysis according to protocol. This study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

10.0 Data Dissemination

This study will be one of the first that we are aware of to assess whether different biomarker measurements tend to be correlated, and to consider whether biomarker values impact on treatment responsiveness. Additionally, this study will be among the first to assess whether having numerous biomarker values available for each patient is preferable to having less information when estimating treatment responsiveness.

The results will be disseminated to the public through publications in peer reviewed journals, alongside abstract presentations at relevant conferences. Authorship will be determined through the ISAR authorship policy.

11.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC). Other members of the committee, as listed in the following table, will form the Advisory Group.

Project Steering Committee Member	**Country/Funder**
Jorge Maspero	Argentina
Mark Hew	Australia
Matthew Peters	
Peter G. Gibson	
Sinthia Bosnic-Anticevich	
Chung, Li Ping	
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12.0 Research Team

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13.0 Timelines

Action	Timeline
Protocol finalisation	October 2021
Ethics approval	November 2021
Dataset preparation	December 2021
Analysis & preliminary results	January 2022
Study report	February 2022
Conference abstract	February 2022
Manuscript	March 2022

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