BLOOD FREE-IgE CONCENTRATION AS A PREDICTOR FACTOR OF RESPONSIVENESS TO ANTI-IgE TREATMENT IN ALLERGIC SEVERE ASTHMA PATIENTS

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DEDICATÒRIA

Als meus pares,
Als meus avis
A la meva dona i al meu fill

AGRAÏMENTS

La present tesi representa el resultat d'anys de dedicació, feina, recerca i passió per una malaltia molt prevalent a la Pneumologia: l'Asma.
Aquest treball no hagués estat possible sense el suport incondicional de diverses persones i institucions a les quals desitjo expressar el meu més sincer agraïment.

En primer lloc, vull agrair al professor i Dr. Christian Domingo i Ribas, director i tutor de tesi, company de feina i mentor. La seva orientació experta i consells han estat fonamentals en cada etapa d'aquest procés. Gràcies per tot l'aprenentatge al llarg dels anys. La seva energia inesgotable i el seu incansable esperit de treball i de superació, han estat una inspiració per acabar aquesta tesi després de tants anys, malgrat tots els entrebancs i amb una pandèmia pel mig que ens va canviar la vida a tots. Gràcies.

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Voldria agrair als meus companys de l'Hospital Universitari de Bellvitge, on vaig iniciar el meu camí en la Pneumologia ja fa 18 anys, el temps passa ràpid, però les amistats i els vincles perduren.

També voldria expressar la meva gratitud a tots els pacients que van participar en els estudis, ja que la seva generositat i voluntat de contribuir a l'avanç del coneixement mèdic, son inavaluables i no seran oblidades.

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I sobretot a Gioconda, la meva dona, amb qui vam començar una bonica història plegats fa uns anys i amb qui en breus iniciarem una nova etapa amb el nostre fill. No tinc paraules per agrair la seva paciència, comprensió i ànim constant. Al teu costat tot es més fàcil. Gràcies, t'estimo infinit.

LIST OF ABBREVIATIONS

ADLs: Activities of daily living
APCs: Antigen-presenting cells
AQLQ: Asthma quality of life questionnaire
ED: Emergency department
Fab: Fragment antigen binding
Fc: Crystallisable fragment
FcεRI: High- affinity receptor
FcεRII: Low-affinity receptor
FENO: Exhaled fraction of nitric oxide
FEV1: Forced expiratory volume in one second
FVC: Forced vital capacity
IgE: Immunoglobulin E
IgG: Immunoglobulin G
IL: Interleukin
ILC2: Innate lymphoid cells type 2
IRB: Internal review board
IU: International Unit
mAbs: Monoclonal antibodies
mDCs: Myeloid dendritic cells
NKT cells: Natural killer T cells
NR-3 criteria: non-responders using FEV1, oral corticosteroid & omalizumab dose
NR-OMA: responders using only omalizumab dose criteria
OC: Oral corticosteroid
pDCs: Plasmacytoid dendritic cells
R-3 criteria: responders using FEV1, oral corticosteroid and omalizumab dose
R-OMA: responders using only the omalizumab dose criteria
Th2: T helper lymphocyte type 2
TSLP: Thymic stromal lymphopoietin
VCAM: Vascular cell adhesion molecule

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SUMMARY

The basis of our current understanding of allergies begins with the discovery of IgE in the mid-1960s. The whole theory of the physiology and pathophysiology of allergic diseases, including rhinitis and asthma, dates from that period. Among the key regions of IgE identified were the Fab (fragment antigen binding) portion that has the ability to capture allergens, and the Cε3 domain, through which IgE binds to its membrane receptor. It was then postulated that blocking IgE at the level of the Cε3 domain would prevent it from binding to its receptor and thus set in motion the allergic cascade. This was the beginning of the development of omalizumab, a monoclonal antibody with an anti-IgE effect. We review the pathophysiology of allergic disease and trace the clinical development of omalizumab. We also review the benefits of omalizumab treatment that are apparently unrelated to allergies, such as its effect on immunity and bronchial remodeling. As a result, it made sense to consider that measuring the amount of blocked IgE by omalizumab (or alternatively the free-IgE concentration) after a certain period of time of treatment, could be a helpful biomarker to predict the response to treatment.

In this prospective study we wanted to determine whether the concentration of free IgE in blood after six months of treatment with omalizumab could predict which patients would show a positive clinical response in the long term. We defined four groups of responders, according to changes in FEV1 value, decreasing dose of oral corticosteroids and omalizumab, and a composite index encompassing all three parameters.

It was observed that the percentage of responding patients according to FEV1 was 45.2%, according to the decrease in the dose of omalizumab 64.5%, according to the decrease in the dose of oral corticosteroids 48.4% and according to the composite index combining the three criteria 77.4%.

Total IgE in blood increased 2.7-fold at month six to decrease at month 30 to 1.8-fold. The percentage of free IgE after six months of omalizumab treatment was 2.33%. The mean free IgE concentration in responder patients did not show statistically significant differences between groups. Consequently, the concentration of free IgE in blood after six months of treatment with omalizumab was not a predictor of response to treatment.

RESUM

La base de la nostra comprensió actual de les al·lèrgies comença amb el descobriment de la IgE a mitjans de la dècada de 1960. Tota la teoria de la fisiologia i fisiopatologia de les malalties al·lèrgiques, incloent rinitis i asma, data d'aquest període. Entre les regions clau d'IgE identificades, hi havia la porció Fab (fragment antigen binding) que té la capacitat de capturar al·lèrgens, i el domini Cε3, a través del qual la IgE s'uneix al seu receptor de membrana. Llavors es va postular que bloquejar la IgE a nivell del domini Cε3 impediria que s'unís al seu receptor i, per tant, s'impediria l'activació de la cascada al·lèrgica. Aquest va ser l'inici del desenvolupament de l'omalizumab, un anticòs monoclonal amb efecte anti-IgE. Revisem la fisiopatologia de la malaltia al·lèrgica i descrivim el desenvolupament clínic d'omalizumab. També revisem els beneficis del tractament amb omalizumab que aparentment no estan relacionats amb les al·lèrgies, com el seu efecte sobre la immunitat i la remodelació bronquial.

Com a resultat, tenia sentit considerar que mesurar la quantitat d'IgE bloquejada per omalizumab (o alternativament la concentració d'IgE lliure) després d'un cert període de temps de tractament, podria ser un biomarcador útil per predir la resposta al tractament.

En aquest estudi prospectiu volíem determinar si la concentració d'IgE lliure en sang després de sis mesos de tractament amb omalizumab podia predir quins pacients mostrarien una resposta clínica positiva a llarg termini. Vam definir quatre grups de resposta, segons els canvis en el valor de FEV1, la dosi decreixent de corticoides orals i omalizumab, i un índex compost que englobava els tres paràmetres.

Es va observar que el percentatge de pacients responedors segons FEV1 era del 45,2%, segons la disminució de la dosi d'omalizumab del 64,5%, segons la disminució de la dosi de corticoides orals 48,4% i segons l'índex compost combinant els tres criteris 77,4%.

La IgE total en sang va augmentar 2,7 vegades al sisè mes, per disminuir al mes 30 en 1,8 vegades. El percentatge d'IgE lliure després de sis mesos de tractament amb omalizumab va ser del 2,33%. La concentració mitjana d'IgE lliure en pacients responedors no va mostrar diferències estadísticament significatives entre grups. En conseqüència, la concentració d'IgE lliure en sang després de sis mesos de tractament amb omalizumab no va ser un predictor de resposta al tractament.

1. INTRODUCTION

In the early 20th century, asthma was classified as either extrinsic and intrinsic. The extrinsic form was identified with allergic asthma. In 1967, a new protein, immunoglobulin E (IgE), was discovered independently by Kimishige and Teruko Ishizaka in Denver, Colorado and by Bennich and Johansson in Uppsala, Sweden, and it was shown to cause allergic processes. The discovery of IgE, and later of specific IgE (IgE developed by the individual against a specific allergen), paved the way for the development of allergy vaccines during the last 25 years of the 20th century. Knowledge of the pathophysiology of asthma (especially early allergic asthma) expanded, disease markers were defined, and asthma phenotypes were described. All of this was linked to the development of new drugs known as biologics (so called because they were originally obtained from live Chinese hamster cells) or monoclonal antibodies (mAbs) [1]. Thanks to the knowledge obtained from the administration of immunotherapy for allergy, IgE took on special importance at the beginning of this process [2]. It was seen that the allergic process began with the activation of dendritic cells or antigen-presenting cells (APCs). The presence of allergens, antigens that favour the production and release of IgE to the medium by plasma cells, promotes the activation of the Th2 pathway, a pathway that requires the differentiation of Th0 lymphocytes (naïve T lymphocytes) into Th2 lymphocytes, and which is able to generate IgE against each allergen to which it is sensitized. This is why this process was called adaptive immunity (i.e., the production of the type of antibody “adapts” to the different allergens with which the individual has been in contact) [3]. As the cell initiating the reaction was the Th2 lymphocyte, the pathway was also called the Th2 pathway. The first monoclonal antibody to be marketed for bronchial asthma was omalizumab, a free IgE blocker [3,4]. Allergen-sensitized IgE-producing patients with clinical symptoms as a consequence of allergen exposure were termed the allergic phenotype.

Subsequently, it was learned that during this Th2 process other molecules known as interleukins (IL5, IL4, IL13) are released into the environment [5]. It has been confirmed that the presence of these interleukins favours, respectively, the synthesis, maturation, and recruitment of eosinophils, the activation of the Th2 pathway, and the blocking of the expression of vascular cell adhesion molecules

(VCAM-1s), and finally the activation of the enzyme that regulates the release of the exhaled fraction of nitric oxide (FeNO), nitric oxide synthase [5].

More recently, it has been observed that apart from this adaptive pathway, the activation of the innate immunity also occurs, which is produced by other molecules: thymic stromal lymphopoietin (TSLP), IL33, and IL25 [1,5]. It was observed that these mediators appear as a result of damage to the bronchial ciliated epithelium, which releases them into the environment [1]. Since they represent an alarm signal warning of epithelial damage, they were named alarmins. This pathway is activated by the effects of different antigens (including allergens which would act in this case by inflammatory and non-allergenic means), and by pollution, tobacco, viruses and bacteria, etc., which damage the bronchial epithelium. This pathway always responds in the same way, thus differentiating it from the adaptive pathway in which the production of specific IgE against each allergen to which the individual is sensitized occurs. Because they are mediated by the innate lymphoid cells type 2 (ILC2), and as an analogy with the allergic cascade which was called Th2 due to the participation of Th2 lymphocytes, the innate and adaptive pathway as a whole were called T2; hence the classification of asthma into T2 and non-T2 [5].

These alarmins directly activate the cells of innate immunity, the ILC2 and the natural killer T cells (NKT cells). These alarmins, especially TSLP, exert control over the activity of antigen-presenting cells. T2 asthma (and perhaps non-T2 asthma) then becomes an epithelium-driven disease [1]. As mentioned above, anti-alarmin monoclonal antibodies are currently being developed [6]. When we administer a mAb, we are modifying the phenotype of the individual, and this causes the organism to try to maintain the lost balance by activating other pathways. We will now describe the scientific and clinical development of the first monoclonal antibody that was marketed two decades ago.

1.1. Structure of IgE

IgE has the structure shown in Figure 1. It has two light chains and two heavy chains. Of special relevance is the Cε3 domain since it is the region through which IgE will bind to its cell surface receptor and is therefore the domain to be pharmacologically blocked. The Cε3 domain is the fraction of the IgE molecule that binds to membrane receptors, and it is the domain to which omalizumab (the anti-IgE antibody) will bind. The key epitope is therefore the Cε3 domain of human IgE [2,3].

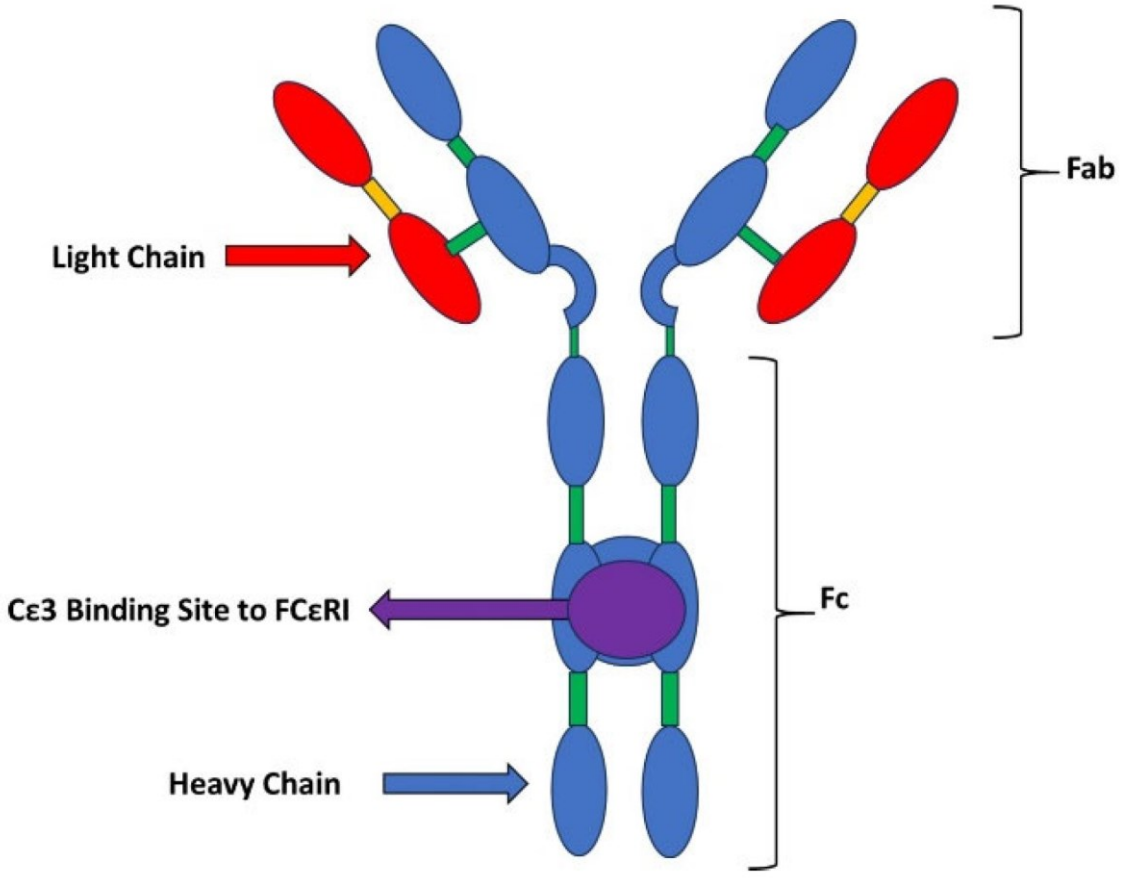


Figure 1. *Structure of IgE (modified from [2]). The Cε3 domain is the fraction of the IgE molecule that binds to membrane receptors. The key epitope is the Cε3 domain of human IgE.*

1.2. Types of IgE

There are two types of IgE: the molecules released into the environment, and those expressed by the cell. In the sensitization process, the cell produces IgE molecules which are released and can be measured in a blood serum test, and these are the ones that will bind to their high- (FcεRI,) and low-affinity (FcεRII) receptors. There is, however, a second type of IgE: the molecules that are not released into the environment and which therefore are not measurable (that is, we cannot determine their presence in a blood test). These are the IgE molecules expressed by the cell. After the first exposure to the allergen and the initiation of the sensitization process, the individual's B cells will now express IgE on their surface rather than IgG (these IgE molecules being very similar to the ones that they will produce and release). Unlike the IgE released into the environment, the B cells produce IgE that have an M1′ domain that allows them to anchor to the cell membrane, but not by binding to the FcεRI receptor. At this time, the B cells are already clearly differentiated (**Figure 2**a,b).

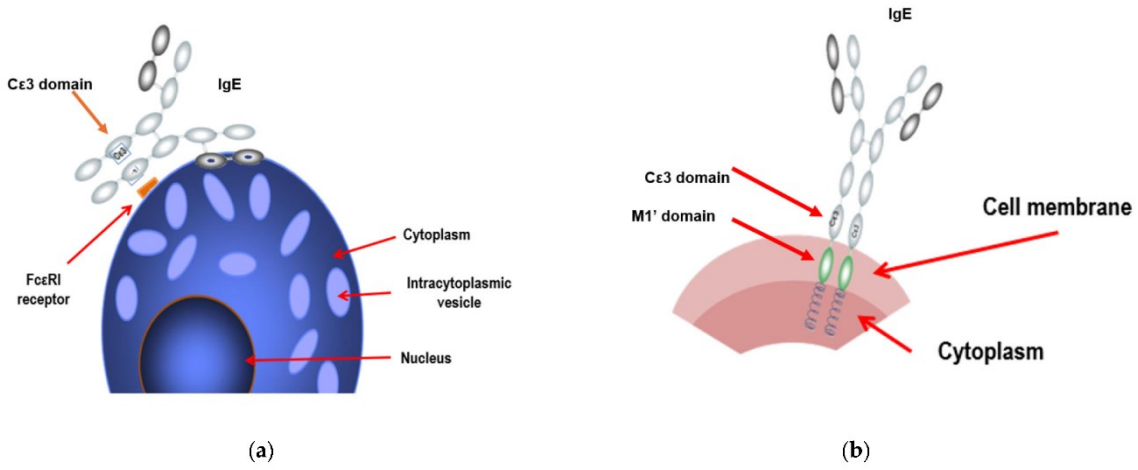


Figure 2. *Types of IgE. There are two types: those secreted into the medium that bind to the cell receptor through the Cε3 domain (**a**) and the non-secreted (or membrane) IgE molecules, which are synthesized and expressed by the cell at the level of its cell membrane (**b**).*

One might think that these cell-expressed IgE molecules do not play any role in the allergic process. However, this is not the case. Allergens that continue to penetrate the organism can follow three pathways: keeping the allergic cascade active by stimulating the process from the dendritic cells; favouring mast cell degranulation as each allergen molecule is captured by two IgE molecules (a cross-linking phenomenon already described above); or stimulating the Th2 pathway by interacting with these membrane IgE molecules. From the therapeutic point of view, although the basic aspect is omalizumab's blockade of the Cε3 domain of the IgE secreted into the medium before binding to receptors, the drug can also bind to the Cε3 domain of the IgE expressed by B cells since, as we have said, they are anchored to the cell surface by the M1′ domain, and therefore the Cε3 domain is free. By binding to this membrane IgE, omalizumab provokes apoptosis of these cells [3].

1.3. Pathogenesis of the Allergic Reaction

When an individual is first exposed to an antigen, dendritic cells (macrophages located in the epithelium of the body) internalize it, process it, and present it to a T-lymphocyte through the major histocompatibility complex type II. In this process, the naïve T lymphocyte can become a T-helper 2 (Th2) or a T-helper 1 (Th1) lymphocyte. The relative amount of each type depends on both the antigen and the host (**Figure 1**) [2].

When the antigen is an allergen, the lymphocyte differentiates into a Th2 cell capable of producing IL-4, which in turn promotes IgE synthesis by B cells. In addition to regulating IgE, IL-4 promotes IL-13 production in mast cells. In their membranes, mast cells contain the high-affinity receptor for IgE (FcεRI). When IgE binds to this receptor, it is ready to block the allergen to which it is sensitized. Up to this point (the sensitization phase), no clinical symptoms have appeared. When two or more IgE molecules that have bound to their receptor recognize the same allergen, they cause the cross-linking effect in the receptors, a phenomenon that triggers a series of biochemical signalling reactions culminating in mast cell degranulation [2,3,4] (Figure 3).

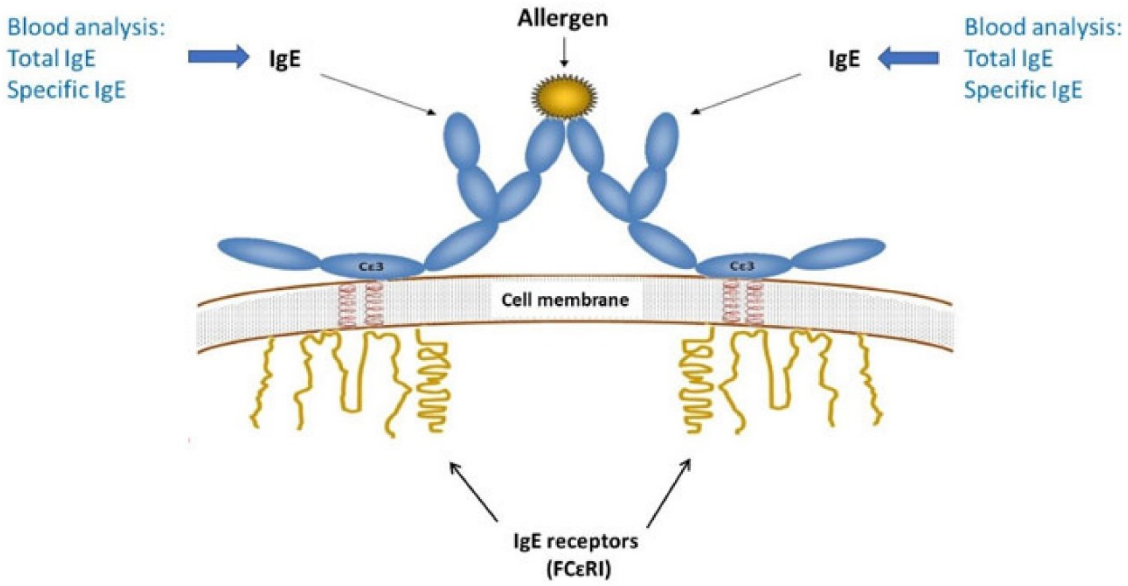


Figure 3. *Acute allergic reaction: cross-linking phenomenon (taken from [5]). The individual is sensitized, produces IgE against the allergen to which s/he is sensitized, and these IgE molecules bind to their membrane receptors on mast cells and basophils. When a new allergen appears, two IgE molecules block the allergen, leading to changes in the intracellular component of the IgE receptor. This will cause mediator-loaded vesicles (in this case histamine) to be released into the environment.*

In the acute allergic reaction phase, the immediate mediators are released. This phase lasts approximately one hour. Subsequently, a second phase may occur after 4–8 h of exposure to the allergen. The chemotactic factors, IL-5, IL-3, IL-13, and cell growth factors released in the immediate inflammation increase eosinophil recruitment. Eosinophils release IL-5, which in turn perpetuates inflammation (the late reaction phase). This can lead to chronic inflammation in cases of continued exposure to the allergen. Occasionally, if the amount of IgE, eosinophils, and other mediators is very high, this process can persist without the need for an allergenic stimulus (chronic phase) [3].

1.4. Importance of Immunoglobulin E

In addition to the role described above, IgE collaborates in other aspects of the allergic reaction that are key elements in the pathophysiology of asthma. As we noted above, IgE binds to its high-affinity receptors, FcεRI receptors, on the surfaces of mast cells and basophils, through the Cε3 domain of its Fc fragment. The correlation between FcεRI expression on basophils and serum IgE levels is well established [6]. IgE itself [7] appears to up-regulate FcεRI expression in human basophils, probably by interacting with FcεRI. Recent data have suggested that IgE has some additional immunobiological effects. This molecule may promote mast cell survival through autocrine production of IL-6 [8]. IgE binds to dendritic cells and enhances allergen uptake and presentation to T cells [9]. Dendritic cells from patients with mild atopic asthma have been reported to bind significantly more IgE than cells taken from healthy individuals [10], and FcεRI receptors are known to be up-regulated on dendritic cells (as well as on eosinophils, mast cells, and macrophages) in patients with seasonal allergic rhinitis [11].

1.5. Omalizumab

The most important step in the production of a monoclonal antibody is the selection of the target. In the case of anti-IgE therapy, the goal is to obtain a specific monoclonal antibody against a key epitope of the IgE molecule. Omalizumab, known in early trials as rhu Mab-E25, is a humanized murine monoclonal antibody that recognizes the Cε3 domain of human IgE, the part of the molecule that binds to mast cell and basophil receptors. Once bound to these cell receptors, IgE undergoes a spatial transformation that favours allergen recognition. This spatial transformation also affects the Cε3 domain and renders it unrecognizable to omalizumab. As a result, omalizumab binds to free IgE but not to IgE bound to cellular receptors [12].

1.5.1. Pharmacological Effects of Omalizumab

Initially, it was observed that omalizumab administration produces a rapid and substantial reduction in free serum IgE, which decreases by 99% within 2 h of administration. It also induces the down-regulation of FcεRI in basophils, dendritic cells, and monocytes within 7 days. At 3 months, the amount of FcεRI receptors on

basophils decreases by up to 93% [13,14]. Therefore, the effect of omalizumab is to reduce both the amount of free serum IgE and the expression of FcεRI on mast cells and basophils. In addition, the decreased expression of FcεRI on dendritic cells may reduce allergen processing and presentation [15], and, consequently, may lead to reduced lymphocyte activation and decreased cytokine production from Th2 lymphocytes. Finally, omalizumab decreases serum, tissue, and sputum eosinophilia. This whole process is summarized in Figure 4.

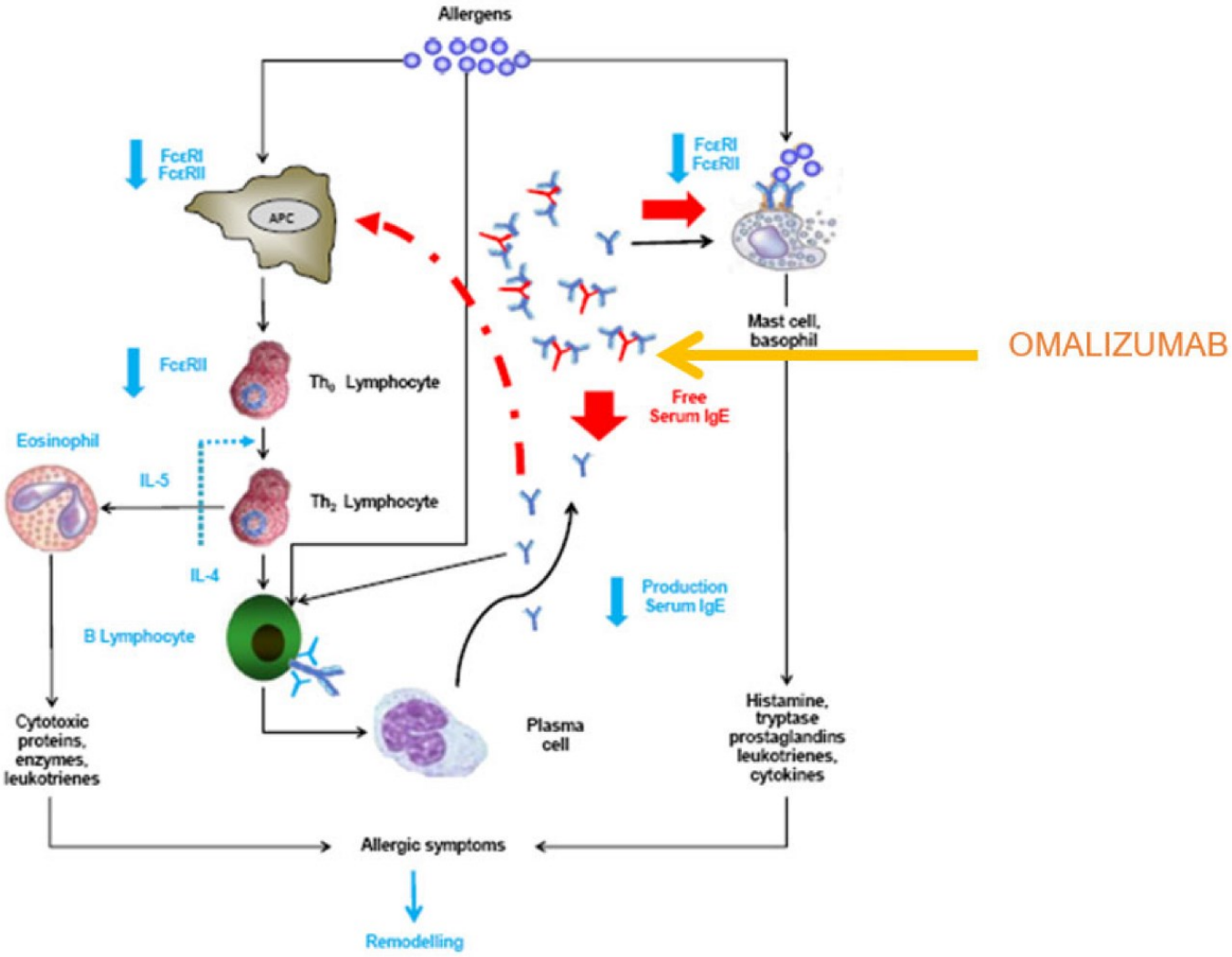


Figure 4. *Effects of omalizumab. The steps of the allergic process are shown in black. The steps blocked by the direct immunoglobulin E (IgE) blocking effect of omalizumab are shown in red. Blue indicates indirect immunomodulation mediated by the action of omalizumab, which causes the down-regulation of the cellular expression of FcεRI, and of FcεRII at different levels, the secretion of interleukin IL-4 and IL-5, and lowers eosinophil*

*and B-lymphocyte levels, as well as IgE production. APC: antigen-presenting cell (modified from [3], Domingo, C. Drugs **2014**, 74, 521–533).*

Subsequently, it was reported that in addition to this direct effect, omalizumab has an immunomodulatory effect, which is shown below:

- Evident reduction of FcεRI expression in mast cells [16].
- Evident reduction of FcεRI expression in basophils [17].
- Decrease in histamine release by basophils [18].
- Reduction in basophils' FcεRI-mediated capacity to release Th2 cytokines [19].
- Decrease in the number of dendritic cells (statistically significant in the case of myeloid dendritic cells (mDCs) and numerical in the case of plasmacytoid dendritic cells (pDCs)) [20].
- Decrease in the number of high-affinity IgE receptors in both pDCs and mDCs in patients with cat allergies [21].
- Decreased dendritic cell-dependent T cell proliferation in co-cultures stimulated with cat allergens [21].
- Significant decrease in the ability of mononuclear cells in culture to release IL-5 [22].

1.5.2. Clinical Development

Despite being the first biologic drug introduced, the development of omalizumab was very well programmed. In addition to its pharmacokinetic effects, the study of its pharmacodynamic effects was very thorough. The pivotal studies and the most important of the many real-life studies are described below.

1.5.2.1. Studies Leading to the Development of Omalizumab

1.5.2.1.1. Pivotal Studies

Table 1 summarizes the most relevant data from pivotal studies focusing on patients with moderate/severe asthma. They show a notable and always significant reduction in exacerbations compared to placebo, and also demonstrate the drug's safety. One of them also reports a marked reduction in inhaled corticosteroid use.

Table 1:

Author	Year	Study	Asthma Severity	Nº of Patients	Efficacy Variable	Results	Duration (Weeks)
Busse [23]	2001	008	Severe	525	Exacerbations	↓48%	28
Solèr [24]	2001	009	Moderate–Severe	546	Exacerbations	↓58–52%	52
Holgate [25]	2004	011	Severe	246	ICS saving	74% of patients ↓ FTC ≥ 50%	32
Vignola [26]	2004	SOLAR	Moderate–Severe	405	Exacerbations AQLQ	38%	28
Ayres [27]	2004	ETOPA	Moderate–Severe	312	Exacerbations / worsening of asthma	↓61%	52
Bousquet [28] *	2004	ALTO	Moderate–Severe	1899	Safety		24
Humbert [29]	2005	INNOVATE	Severe	419	Exacerbations	↓50%	28

Undoubtedly, the most significant study is the INNOVATE study, which reported the following:

- A 50% reduction in severe exacerbations.
- A 44% reduction in emergency room visits.
- An improvement in the quality of life assessed by the AQLQ (asthma quality of life questionnaire), both in the overall score and in the various dimensions. The overall difference was statistically significant compared to placebo, although it did not reach the clinically relevant value of 0.5.

1.5.2.1.2. Real-Life Studies

Two real-life studies of omalizumab, one by Braunstahl (eXpeRience) [30] and one by Korn [31], stand out. The eXpeRience study was an international, open-label, single treatment arm, 2-year study involving 14 countries in Europe, the US, and Asia, and designed to evaluate the effectiveness of omalizumab. It included 943 patients with uncontrolled allergic asthma. Among the most noteworthy results were the following:

- The limitation in activities of daily living (ADLs) was reduced from 4.4 days per week to 1.3 and 1.2 at one and two years of follow-up, respectively.
- A decrease in the use of rescue medication that ran parallel to the improvement in ADLs. Consumption fell from 4.8 days per week to 1.8 and 1.6 at one and two years of treatment, respectively.
- The average annual days off work fell from 26.4 before the start of treatment with omalizumab to 3.5 and 1.0 days after one and two years of treatment with omalizumab, respectively.
- An increase in the percentage of patients without clinically relevant exacerbations (either severe or non-severe).

1.5.2.2. Specific Aspects of the Development of Omalizumab

1.5.2.2.1. Fall in Exacerbations

The INNOVATE study [29] showed that the rate of clinically significant exacerbations (the primary efficacy endpoint), adjusted for an observed imbalance in exacerbation history, was 0.68 with omalizumab and 0.91 with placebo, representing a 26% reduction during the 28-week treatment phase. Without adjustment, a similar magnitude of effect (a 19% reduction) was observed, although it did not reach statistical significance. The CHOC study (Clinical and Histological impact of treatment with Omalizumab in severe allergic oral Corticosteroid dependent allergic asthma patients) [32] reported a 54% reduction in total exacerbations. For severe exacerbations, the INNOVATE study [29] showed an annualized reduction of 50%. In the CHOC study [32], none of the patients treated with omalizumab had severe exacerbations during follow-up, and exacerbation duration was reduced by half.

Two real-life studies involving oral corticosteroid (OC)-dependent patients (the eXpeRience registry [30], with 28.1% of patients receiving OC, and the Xpertise trial [31], with 46%) showed reductions in exacerbations of more than 80%.

In addition to exacerbations, some studies have measured emergency department visits or hospitalizations. The INNOVATE study [29], in which OC-dependent patients represented 22% of the sample, showed a 44% annual reduction in emergency room visits. In a real-life study, Molimard et al. [33] found a 65% reduction in annual ED visits after treatment with omalizumab. In Germany, in a

population of 280 patients, 46% of whom were cortico-dependent, Korn et al. [31] reported an 82% reduction in exacerbations and a 78% reduction in hospitalizations.

1.5.2.2.2. Corticosteroid Sparing Capacity

The Cochrane review [34] concluded that treatment with omalizumab was associated with a significant possibility of reducing inhaled corticosteroid doses or of withdrawing them completely. The mean dose reduction was −118 µg beclomethasone dipropionate equivalents. In the subgroup of patients receiving OCs, it was unclear whether this benefit occurred. In a subgroup analysis in an open-label parallel-group study, Siergiejko et al. [35] found that at week 32, 62.7% of patients in the treated group were able to discontinue or reduce OCs compared with 30.4% of controls. The real-life eXpeRience study [30] found a relative reduction of 50% at month 24, and the APEX study, a retrospective study conducted in the UK, found a 34% reduction in the mean total amount of prescribed OCs per year and complete cessation of OC use after 12 months in 48% of patients [36]. In a 2-year prospective observational study, Domingo et al. [37] reported that omalizumab allowed OC withdrawal in 74.2% of patients. Real-life studies are usually understood to obtain better results than randomized clinical trials, but the CHOC study [32] presented results of the same order as the best real-life studies. In this open randomized study, it was observed that 12 patients (75%) in the omalizumab group and only one (7.7%) in the control group were able to cease OC treatment.

1.5.2.2.3. Biomarkers Predicting Response to Omalizumab

The biomarkers that have been evaluated are the exhaled fraction of nitric oxide (FeNO), peripheral blood eosinophils, peripheral blood immunoglobulin E (IgE) concentration, and, in experimental studies, the blood periostin value. An early study by Djukanovic [14] in 45 patients with mild/moderate asthma, who were divided into two groups of 22 (omalizumab) and 23 (placebo), showed at 16 weeks that treatment with omalizumab decreased the number of eosinophils in patient sputum (from 6.6% to 1.7% in the treated group; $p = 0.05$) versus a non-significant decrease in the placebo group (from 8.5% to 7.0%). This decrease was also observed in bronchial biopsy specimens.

The EXTRA study [38] found the patients with the lowest incidence of exacerbations to be those with FeNO values ≥ 19.5 ppb, eosinophils ≥ 260 µL, and periostin ≥ 50 ng/mL.

Eosinophil rates may be elevated in allergic patients without the patient exhibiting an eosinophilic phenotype. There is some controversy as to whether this biomarker can condition the response to treatment with omalizumab. A study by Casale et al. [39] also showed that the baseline eosinophil level, as well as other clinical markers, predicted response to omalizumab. Patients with a history of frequent ED visits, hospitalizations, FEV1 (%) values < 65%, beclomethasone dipropionate doses of ≥600 µg, and who use long-acting beta-agonists (LABAs) are the best responders to omalizumab. The STELLAIR retrospective study [40], conducted in France, included 872 patients (723 adults and 149 non-adults aged 6–17 years) with severe allergic asthma who were treated with omalizumab by 78 physicians. The mean eosinophil count was ≥300 cells-µL-1 in 52.1% of the adults and in 73.8% of the children/adolescents. The percentage of responders did not vary in the subgroups established according to the baseline eosinophil value, leading the authors to suggest that the eosinophil level is not a good predictor of response to omalizumab. Finally, it has been speculated that omalizumab may have a long-term effect on IgE synthesis. Lowe and Renard [41] obtained data on omalizumab and free and total IgE from an epidemiological study and from six randomized, double-blind, placebo-controlled trials in patients with allergic asthma. IgE production and clearance were modelled, and it was concluded that after five years of treatment, IgE production decreases. In a study in which free IgE and total IgE (free + blocked with omalizumab) were measured, Domingo et al. [42] observed a decrease in IgE production. This result appeared to justify the discontinuation of treatment after five years, but this biological observation did not correspond to the clinical findings and cannot therefore be used as a criterion for stopping treatment.

1.5.3. Long-Term Tolerance

When a new drug is introduced, one of the key aspects is its safety. The EXCEL study [43,44], conducted at the request of the FDA, was a post-marketing study that included 4972 patients treated with omalizumab and 2867 patients who were not treated. It demonstrated the safety of the drug, but raised doubts about the incidence of neoplasms, which appeared to be higher in the treated group. The increased risk was attributed to the fact that the treated group was followed for a longer time. Subsequently, a study by Long et al. [45] showed that omalizumab treatment does not increase the incidence of malignancies. A recent retrospective study in 45 patients with a mean follow-up of 10.6 ± 1.2 years [46] has also shown the effectiveness and safety of the drug.

1.5.4. Withdrawal of Treatment

An early study showed that after omalizumab withdrawal, symptoms reappear and are accompanied by an increase in free IgE [47]. Subsequently, Molimard et al. [48] observed a loss of asthma control in 55.7% of patients 13 months after treatment withdrawal. After six years of treatment, Kupryś-Lipińska and Kuna [49] observed that 9/11 (81.8%) presented exacerbations within five months of treatment withdrawal. A study by Nopp et al. [50] in a population of cat epithelium allergic individuals demonstrated that three years after withdrawal from a six-year treatment programme with omalizumab, there was no loss of respiratory function. In the XPORT study [51], a randomized study with two treatment groups (a minimum of five years with omalizumab versus placebo) showed that patients who continued with omalizumab had better asthma control during the 52 weeks of the study. Vennera et al. [52] observed that despite five years of treatment with omalizumab, the number of patients with severe exacerbations increased over time, with 39% of patients presenting severe exacerbations four years after discontinuation of treatment. The OMADORE study [53] is the only study that has proved able to identify patients in whom omalizumab can be safely withdrawn. Among the patients who met the clinical stability criteria and whose FEV1% did not deteriorate after 18–24 months of treatment, those who tolerated the decrease did so between 18–40 months after starting treatment; they tended to be younger and have better GETE, improved FEV1% after the first dose of omalizumab, reduced oral corticosteroid use, and FeNO values < 50 ppb. With this protocol, omalizumab could be withdrawn in

approximately one third of patients, without severe exacerbations occurring during the following 30 months. More recently, in a retrospective study in France based on information from a national health service data registry, 16,750 adults and 2452 children (age ≥ 6 years) were identified with median periods of omalizumab treatment before withdrawal of 51.2 and 53.7 months, respectively. Among the adults who discontinued omalizumab when their asthma was controlled, 70%, 39%, and 24% remained controlled and did not resume omalizumab treatment one, two, and three years after discontinuation, respectively [54].

1.5.5. Particular Effects of Omalizumab

In addition to the descriptions above, numerous studies have revealed other unexpected effects of the drug.

1.5.5.1. Omalizumab and Remodelling

Information on remodelling and biologic treatments in patients with severe asthma is limited and often indirect. Omalizumab has been shown to decrease endothelin-1 clearance in exhaled air [55], reduce bronchial wall thickness, and increase the bronchial endoluminal area [56]. Two ex vivo studies have shown that the presence of IgE induces extracellular matrix and collagen deposition and antagonizing IgE reverses these effects [57,58]. The only study to demonstrate the reversibility of remodelling in the ciliated epithelium (including the reappearance of cilia) and reductions in intracellular spaces and in the thickness of the basement membrane is the CHOC study [32].

1.5.5.2. Omalizumab and Infections

Among the factors that predispose patients to the triggering of asthma exacerbations are respiratory infections of viral origin, which lead to peaks of exacerbations throughout the year. This is clearly evidenced in the study by Johnston et al. [59].

The possibility that there might be a relationship between the presence of IgE molecules and their binding to their high-affinity receptors and lung infections was raised when a decrease in interferon production was observed in patients with asthma infected by the influenza virus; in this situation, there was an inverse

relationship between IgE blood concentration and interferon production [60]. It was suggested that the production of interferon by plasmacytoid dendritic cells might be down-regulated due to the binding of free IgE molecules to their high-affinity receptors upon the activation of a cascade that blocks the order sent from toll-like receptors stimulated by the presence of viral genetic material (Figure 5).

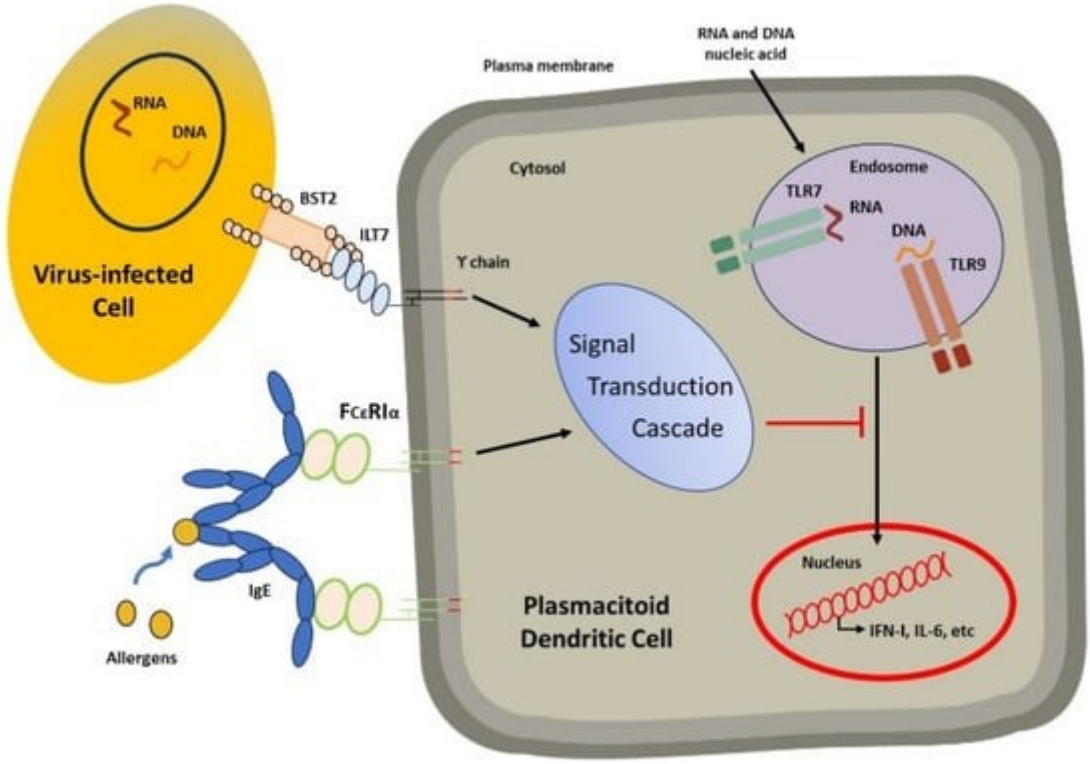


Figure 5. *Modified from Lynch et al. [61]. The figure shows how IgE molecules bind to their receptors and are ready for the cross-linking phenomenon to occur in the presence of allergens. This will activate the cascade that blocks the command sent from the toll-like receptors for the nucleus to synthesize interferon.*

If all this is true, it makes sense to examine whether blocking IgE might stop the cross-linking phenomenon, and whether interferon production in the presence of viral genetic material would therefore remain intact. This possibility was clinically confirmed by the ICATA study [62], which showed that treatment with omalizumab improves the control of allergic asthma, prevents seasonal exacerbations, and reduces the consumption of inhaled corticosteroids.

The PROSE study confirmed that the addition of omalizumab 4–6 weeks before the start of the school year and maintained for the following four months reduced

exacerbations more than in the placebo group and in the group that received a reinforcement of inhaled corticosteroids, since it contributed to restoring the defensive mechanisms [63]. This benefit also seems to extend to asthmatic children with more severe disease [64].

1.5.6. Omalizumab and Pregnancy

Information on the use of omalizumab during pregnancy is limited. However, the Expect registry [65] collected information from 230 pregnant women (64.9% with severe asthma and 35.1% with moderate asthma) treated with omalizumab from 2006 to 2017 in the US and compared these data with those obtained from a cohort of 1153 women from Quebec (21.2% with severe asthma and 78.8% with moderate asthma) who were not treated with omalizumab, which served as a control. The study concluded that omalizumab can be safely administered to pregnant women, and that it does not increase the risk of malformations in the fetus or the risk of small size for gestational age.

1.5.7. Indication of Omalizumab

The drug is indicated in patients with severe allergic asthma. Certain factors regarding the initial indication and subsequent modifications should be borne in mind (see Table 2) [3].

Table 2. Criteria for indication of omalizumab at the start of marketing and subsequent modifications.

	At Marketing	Post-Marketing Modification
Age (years)	≥12	≥6
Allergy sensitization	Positive skin prick test or in vitro reactivity to at least one perennial aeroallergen	Positive skin prick test or in vitro reactivity to at least one perennial aeroallergen
Baseline immunoglobulin E level	≥30–700 kU/L	≥30–1500 kU/L
Monthly calculated omalizumab dose	≤750 mg	≤1200 mg
Asthma severity	Severe or inadequately controlled asthma	Severe or inadequately controlled asthma
Re-evaluation	After 16 weeks of treatment	After 16 weeks of treatment
Long-term treatment withdrawn	Not specified	Not specified

It has also been observed that omalizumab is effective in patients with severe allergic asthma who have been sensitized to seasonal allergens [66]; however, this indication does not appear on the technical data sheet. Other exploratory indications include the administration of the drug as a preventive treatment in cases of immunotherapy for venoms [67] or in exercise-induced anaphylaxis [68]. These prescriptions should be made in specialized units.

1.6. Conclusions

Omalizumab has had an exemplary theoretical and practical development. By blocking IgE, a molecule that is undoubtedly central to the development of allergic reactions, it has led to a better understanding of the Th2 pathway and has contributed to the concept of T2 inflammation. The exemplary development of omalizumab over the past 20 years has enabled shorter development times for other monoclonal antibodies that block molecules such as the interleukins IL5, IL4, and IL13 and the alarmins TSLP, IL33, and IL25.

2. HYPOTHESIS

Free IgE blood concentration after six months of treatment with omalizumab, can be a predictor of asthma response.

2.1. Rational of the study

When an atopic individual is exposed to an antigen, the dendritic cells (macrophages located in the organism's epithelium) internalize it, process it and present it to a T lymphocyte, via the major histocompatibility complex. In this process, the T-lymphocyte develops a T_h2 or a T_h1 profile. When the type of antigen is an allergen, the lymphocyte differentiates into a T_h2 cell able to produce IL-4 which in turn promotes the synthesis of IgE by the B-lymphocytes [2]. In these subjects, exposure to high concentrations of allergens leads to a high concentration of serum IgE which favours the appearance of allergic symptoms.

The rationale for the use of omalizumab is based in the IgE blocking effect of this drug which inhibits part of Th2 immune response, thus reducing recruitment and activation of effector cells of the inflammatory process, including eosinophils [3, 69]. Because IgE effector cells, such as mast cells and basophils are a source of pro-inflammatory chemokines, cytokines, and proteases, anti-IgE therapy has anti-inflammatory effects in asthma and other diseases [2]. Omalizumab has shown to produce a free serum IgE fall by 99% within two hours, a downregulation of IgE receptors on basophils, mast cells and dendritic cells after three months, a reduction of the number of eosinophils in sputum and bronchial biopsies, a reduction of exhaled nitric oxide and a downregulation of the IgE production [2, 3]. Some studies have shown the antiallergic and anti-inflammatory properties of omalizumab, such as the reduction in circulating, tissue, and sputum eosinophils [18, 70] sometimes due to an increase in eosinophil apoptosis and a decrease in granulocyte-macrophage colony stimulating factor (GM-CSF, IL-2 and Il-13).

Omalizumab treatment cannot be monitored by total blood IgE since the drug binds to IgE (2 molecules of omalizumab bind to one molecule of IgE) thus causing trimers and examens to be eliminated more slowly from the blood. Moreover, omalizumab

is an IgG1 with a half-life ranging between 21-23 days while IgE half-life is around 2-3 days. As a result, there is a higher concentration of IgE in the blood of treated patients even though most of it is inactivated. Last but not least, the fraction of blood free IgE could not be measured in patients treated with omalizumab until quite recently [71].

The purpose of this study is to elucidate in a cohort of corticosteroid-dependent allergic asthma patients treated six months with omalizumab whether the fraction of IgE non bound to omalizumab can predict the clinical response of a patient.

3. OBJECTIVES

The main objective is to assess the predictive capacity of free immunoglobulin E (IgE) concentration after six months of treatment with omalizumab, on the response to treatment with omalizumab in severe allergic asthma patients.

The secondary objectives are the following:

1. To establish the percentage of responding patients according to FEV1, omalizumab dose, oral corticosteroid dose and a composite index combining the three criteria.

2. To describe the evolution of total IgE after 30 months of treatment with omalizumab.

3. To measure the mean free IgE concentration in responder patients according to FEV1 value, dose of omalizumab and oral corticosteroids and the composite index that combines the three previous criteria.

4. To determine the percentage of free IgE after six months of treatment with omalizumab, and its capacity as a predictor of response to treatment.

4. METHODS

4.1. Setting

Corporació Parc Taulí (CPT) (Sabadell/Catalonia), a 760-bed university hospital.

4.2. Design

Unicenter, prospective observational study.

4.3. Study population

Patients were recruited from the severe asthma unit of our hospital [72]

4.4. Inclusion criteria

a) Age ≥ 18 years old
b) Airway reversibility (FEV_1 reversibility ≥ 12% and 200 mL)
c) Positive skin-prick test or in vitro reactivity (Immunecap) + allergic symptoms.
d) Baseline Immunoglobulin E level ranking between 30-1500 IU/mL.
e) Patient weight between 25 and 150 kg.
f) Patients naive to biologic treatments
g) Oral corticosteroid-dependence due to asthma is defined either as a requirement of a mean daily dose of at least 5 mg per day of prednisolone to maintain a forced expiratory volume in the first second (FEV_1) > 50% during a period of one year or more in addition to the best standard care (BSC) provided by GINA or as repeated boosters (≥ 5/year with an accumulated oral corticosteroid dose ≥ 300 mg/episode) during the previous year
h) Patients eligible for omalizumab treatment
i) A written informed consent obtained from every patient.

4.5. Exclusion criteria

a) Patient refusing to sign the written informed consent.
b) Hypersensitivity to omalizumab
c) Patient unable to regularly attend the asthma unit for control and drug administration.

4.6. Sample size

There are no previous estimations in the literature. We considered that a cohort of 30 patients would be representative for a pilot study.

4.7. Methods

Treatment protocol: BSC following the recommendations of the GINA. Prior to starting omalizumab treatment, patients will have gone a stabilization period of at least three months.

The protocol followed for decreasing oral corticosteroid administration can also be found elsewhere [37].

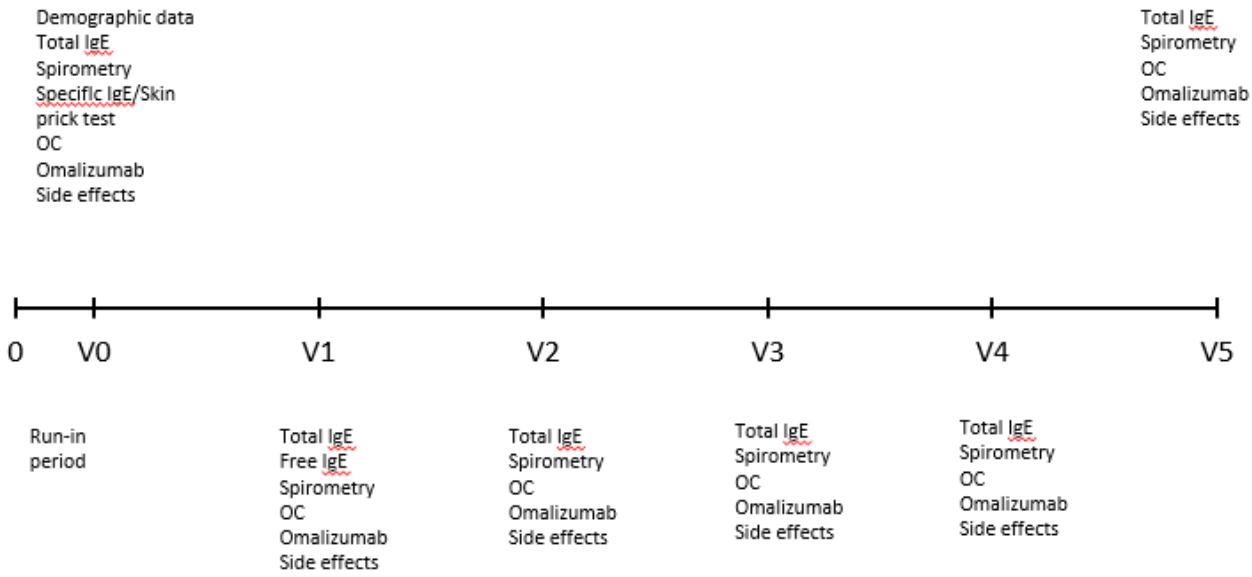
The dose decreasing protocol followed was the OMADORE, that can be found elsewhere [53].

At the end of the stabilization period, there was a one-month run-in period, after which the protocol was initiated.

4.8. Study protocol

Total IgE concentration were measured at entry and at every six months. Free IgE were measured at visit one (V1: six months of treatment of omalizumab). At every visit a forced spirometry was performed. Oral corticosteroid and omalizumab dose were registered. See Figure 6.

Figure 6: *Study protocol*



OC: oral corticosteroids

4.9. Informed consent

- A written Informed Consent was obtained from every patient. (Appendix 10.2)
- Patients' information sheet: an information sheet was given to patients (Appendix 10.3)
- Patients' Information Sheet for sample release (Appendix 10.4)
- Patients' Informed Consent for sample release (Appendix 10.5)
- The protocol was approved by the internal review board (IRB) of the hospital. (Appendix 10.6)

4.10. Definitions

A patient was considered a responder if he met at least one of the following criteria:

- FEV_1 at the follow-up visit > FEV_1 at visit 0
- Dose of corticosteroids at visit 5 < Dose of corticosteroids at visit 0
- Dose of omalizumab at the follow-up visit < Dose of Omalizumab at visit 1.
- The composite index combined all three criteria.

4.11. Side-effects monitoring

Patients were specifically asked about side-effects at each visit. They were also given the telephone number of the outpatient unit of the pulmonary service and told to report any suspected side-effects.

4.12. Instrumentalization

All tests were performed according to the hospital regular practice

4.12.1. Free IgE measurement techniques in patients treated with omalizumab

The FcεRI ectodomain will be fused with avian IgY constant domains, recombinantly produced in HEK293 cells and assessed for proper folding and specific binding to human and murine IgE by immunoprinting and ELISA. Competition with omalizumab and the potential for allergen-specific detection will be addressed by ELISA. The free IgE levels of patient sera will be analysed using this FcεRI-IgY chimera as a capturing agent.

4.12.2. Assessment of immunoreactivity in ELISA

For assessment of immunoreactivity purified FcεRI fusion proteins (diluted in 1% (w/v) BSA in phosphate buffered saline, PBS) will be applied to microtiter plates previously coated with 100 µg/mL of monoclonal antibodies of different isotypes (18, 19) at 4° C overnight and blocked with 2% (w/v) BSA-PBS at RT for 2 h. After incubation for 90 min at RT on a rocker platform, the wells will be rinsed 3 times each with 0.1% (v/v) Tween-PBS and PBS and further incubated with 100 µl of an anti-IgY (Fc-specific) alkaline phosphatase conjugate (diluted 1: 10000 in 1% (w/v) BSA-PBS, Rockland, Gilbertsville, PA, USA) for 60 min at RT on a rocker platform. The wells will be rinsed again 3 times with 0.1% (v/v) Tween-PBS and PBS and bound antibodies will be visualized by addition of 75 µl of an 2,2-azino-bis(3-ethyl-benzothiazoline-6-sulfonic acid) di-ammonium salt (ABTS) substrate solution (Sigma-Aldrich, Taufkirchen, Germany). Absorbance will be determined at 405 nm after 15 min of incubation.

For determination of serum IgE 100 µl of FcεRIε-IgY constructs (0.5 µg/mL in PBS) or omalizumab (10 µg/mL) will be immobilized on microtiter plates. After incubation

at 4° C overnight the wells will be rinsed with wash buffer (reagent set B, BD Pharmingen, San Diego, CA, USA). Then, dilutions of human myeloma IgE (Calbiochem, Nottingham, UK) or serum samples will be added and incubated for 2 h at RT. For competition experiments, a constant myeloma IgE concentration of 10 ng/mL will be used in the presence of omalizumab at concentrations ranging from 0.02-200 µg/mL. After washing 100 µl biotinylated mouse anti-human IgE (BD Pharmingen, 1:250 in assay diluent) and streptavidin-HRP conjugate (BD Pharmingen, 1:1000 in assay diluent) will be added and further incubated for 1 h at RT. The wells will be rinsed again and bound IgE will be visualized by the addition of 75 µl of an ABTS substrate solution (Sigma-Aldrich). Absorbance was determined after 15 min and addition of 50 µl stop solution at 450/750 nm. Allergen-specific IgE will be detected by addition of biotinylated allergen extracts (Siemens Healthcare Diagnostics, Los Angeles, CA, USA) and streptavidin-HRP conjugate (BD Pharmingen, 1:1000 in assay diluent).

Quantitation of FcεRIε-IgY constructs will be determined by sandwich ELISA (Chicken IgG Quantitation Kit, Biomol, Hamburg, Germany) according to the recommendations of the manufacturer.

4.13. Statistical analysis

All study variables were described by frequencies and percentages over the valid N for categorical variables and by measures of central tendency and dispersion for continuous variables (mean and standard deviation [SD] for those with normal distribution, and median and percentiles 25% [P25] and 75% [P75] otherwise). The symmetry of continuous variables was evaluated with the Shapiro-Wilk test. The valid N was reported for all variables. Longitudinal measures were described by follow-up visit.

Bivariate analysis. All study variables were described and compared by treatment response at visit 5. Comparisons were performed using the definition of treatment response based on the three criteria indicated in the Primary outcome section. Additionally, comparisons were also performed using the omalizumab criterion only. Comparisons between responders and non-responders were performed with the Pearson $\chi 2$ test, the t test or the Mann-Whitney U test.

Analysis of the main objective: The predictive capacity of free IgE at visit 1 and of the free/total IgE ratio at visit 1 for the response to treatment at visit 5 was evaluated by calculating the area under the ROC curve (AUC) and its 95% confidence interval (CI). The cut-off point maximizing sensitivity with a minimum specificity of 0.9 was obtained

4.14. Study restrictions

This is a pilot study.

5. RESULTS

5.1. Sociodemographic characteristics

We recruited 31 patients (21 women; 10 men) and there were no losses. All of them finished the follow-up. Demographic and initial clinical data are summarized in table 3.

Table 3: Sociodemographic characteristics

Variable	Statistic	Valid N
Sex, n (%):		31
Women	21 (67.7%)	
Men	10 (32.3%)	
Age at visit 0 [years], Mean (SD)	51.7 (17.0)	31
Weight [kg], Mean (SD)	73.0 (17.9)	31
Height [cm], Mean (SD)	160 (9.76)	31
BMI [kg/m^2], Mean (SD)	28.3 (6.00)	31
Total IgE [IU/mL], Mean (SD)	285 (280)	31
FVC [%], Mean (SD)	77.4 (20.1)	31
FEV_1 [%], Mean (SD)	63.5 (20.5)	31
FEV_1/FVC ratio [%], Mean (SD)	62.9 (14.2)	31
Dose of corticosteroids [mg], Mean (SD)	5.74 (5.13)	31

BMI, body mass index. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IU, international unit.

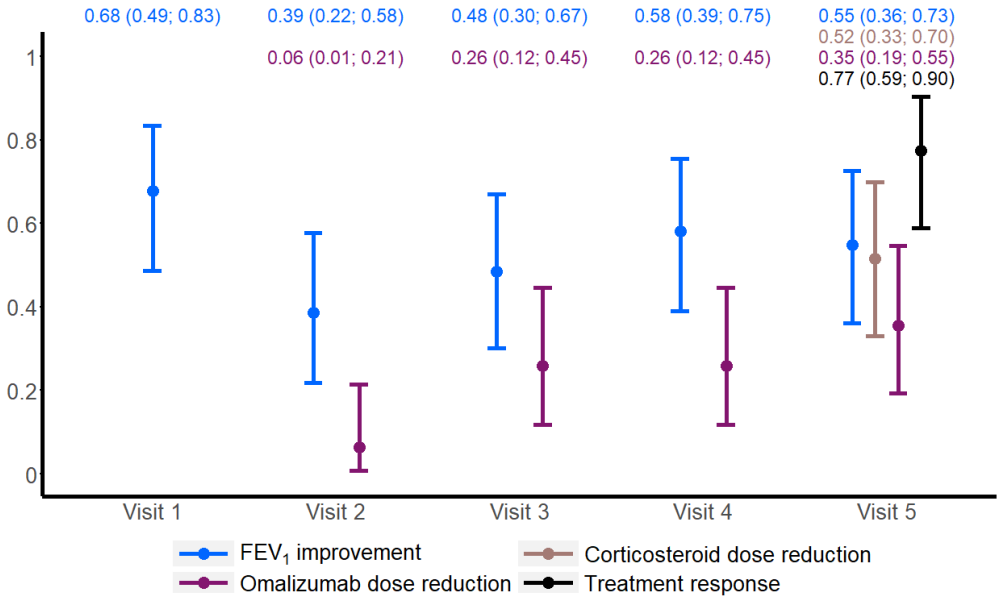
The data show that patients were allergic and eligible for anti-IgE treatment (mean total IgE 285 IU; mean daily OCS dose 5.74 mg; mean FEV1 value 63.5%). No confounders clinical characteristics were present (BMI 28.3 kg/m^2).

5.2. Longitudinal measures

The longitudinal follow up results for the whole group are shown in table 1s (Appendix 7) and figure 6 (see below).

The IgE concentration increased 2.7-fold from baseline at visit 1, and then fell progressively to 1.8 times the baseline level by the end of the follow-up. After six months of treatment with omalizumab, 97.67% of IgE was blocked. For the whole group, the dose of omalizumab fell by 18% and the dose of OCs by 39.3%.

Figure 6: *Evolution of the treatment response criteria throughout follow-up visits.*



This figure shows the proportion of responders at every visit according to the different criteria used. The complementary proportion represents the non-responders. Detailed data can be found in table-support materials in Appendix 7.

The percentage of responders according to the different criteria used is summarized in table 4 and tables 2s (three criteria) and 3s (omalizumab criteria).

Table 4: Percentage of responders according to the response criteria

	FEV1	Omalizumab	Oral corticosteroids	Three criteria
Responders	14 (45.2%)	20 (64.5%)	15 (48.4%)	24 (77.4%)
Non-responders	17 (54.8%)	11 (35.5%)	16 (51.6%)	7 (22.6%)

For the composit index including the three criteria (see table 4 above) a 77.4% of responders was found.

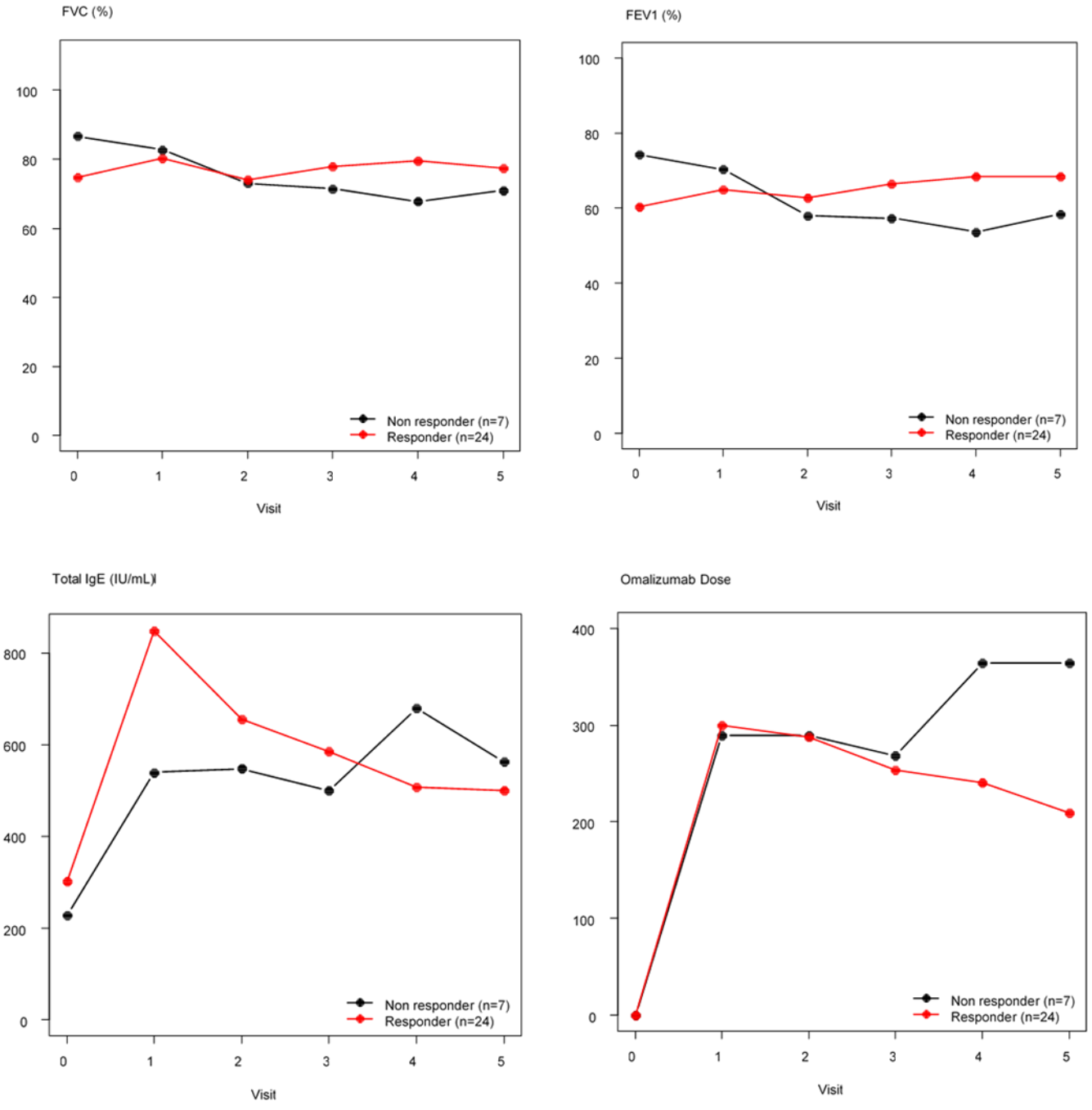
When absolute values were compared (see appendix 7, table 2s):

- The OCs dose showed numerical differences (initial/end responders: 6.5/2.08 mg; initial/end non-responders: 3.14/3.14 mg; p=NS). The comparison reached a statistical significance when it was made between the percentage of responders and non-responders for OCs dose changes (p= 0.002).
- Some numerical improvement in spirometry was observed (initial/end percentage of FEV1 non-responders: 74.1/58.3%; initial/end percentage of FEV1 responders: 60.4/68.3%) that reached statistical differences when percentage of responders and non-responders was compared (p=0.002).
- Regarding omalizumab dose, there were numerical differences (initial/end dose for the non-responder 289/364 mg and initial/end dose for responder 300/209 mg) that showed a trend to statistical significance (p=0.057), that was confirmed when percentage comparison was made (65/35%; p=0.072). Responders presented higher IgE concentrations at baseline. At visit 5, it is the opposite. These data are represented in figure 7. The same comparisons using the free IgE at month 6 and the ratio free IgE/ total IgE were performed but did not reveal any differences (tables 5 and 2s; figures 8 and 9).

When only the omalizumab dose was used as a response criterion (see appendix 7, table 3s):

- At visit 3, a statistical trend in omalizumab dose decrease was already detected favouring the responder group (p=0.056).
- At visit 5, the non-responder/responder dose difference (319/109 mg) was statistically significant (p<0.001). This was confirmed when the comparison of percentages was performed.
- Regarding OCs dose, there was a trend to statistical differences between non-responder/responder (visit 5: 3.10/0.91 mg; p= 0.071) that reached statistical differences when comparison between the percentage of omalizumab non-responder/responder was made:
    - Omalizumab non-responders: OCs dose non-reduction (65%) vs reduction (35%).
    - Omalizumab responders: OCs dose non-reduction (18%) vs reduction 81.8%) p= 0.034.

Figure 7: Evolution in the FVC, FEV1, IgE and omalizumab dose according to their response (three criteria).



The numerical data can be found in appendix 8

5.3. Total IgE and Free IgE fraction

A description of IgE (total and free fraction) are shown in table 5.

Table 5: Description of the initial and final free and total IgE values and spirometric evolution.

	Total	NR-3 criteria	R-3 criteria	NR-OMA	R-OMA
IgE-0 (IU/mL)	285	227	301	271	310
IgE-5(IU/mL)	514	563	500	589	378
Free IgE -1 (IU/mL)	6.62	3.2	7,62	8.06	4.01
FEV1-0 (%)	63	74	60	65	64
FEV1/FVC-0 (%)	63	66	62	61	65

- NR- 3 criteria: non-responders using the FEV1, oral corticosteroid and omalizumab dose.
- R-3 criteria: responders using the FEV1, oral corticosteroid and omalizumab dose
- NR-OMA: responders using only the omalizumab dose criteria
- R-OMA: responders using only the omalizumab dose criteria

Figure 8: The concentration of free IgE in different settings is shown in figures A-D.

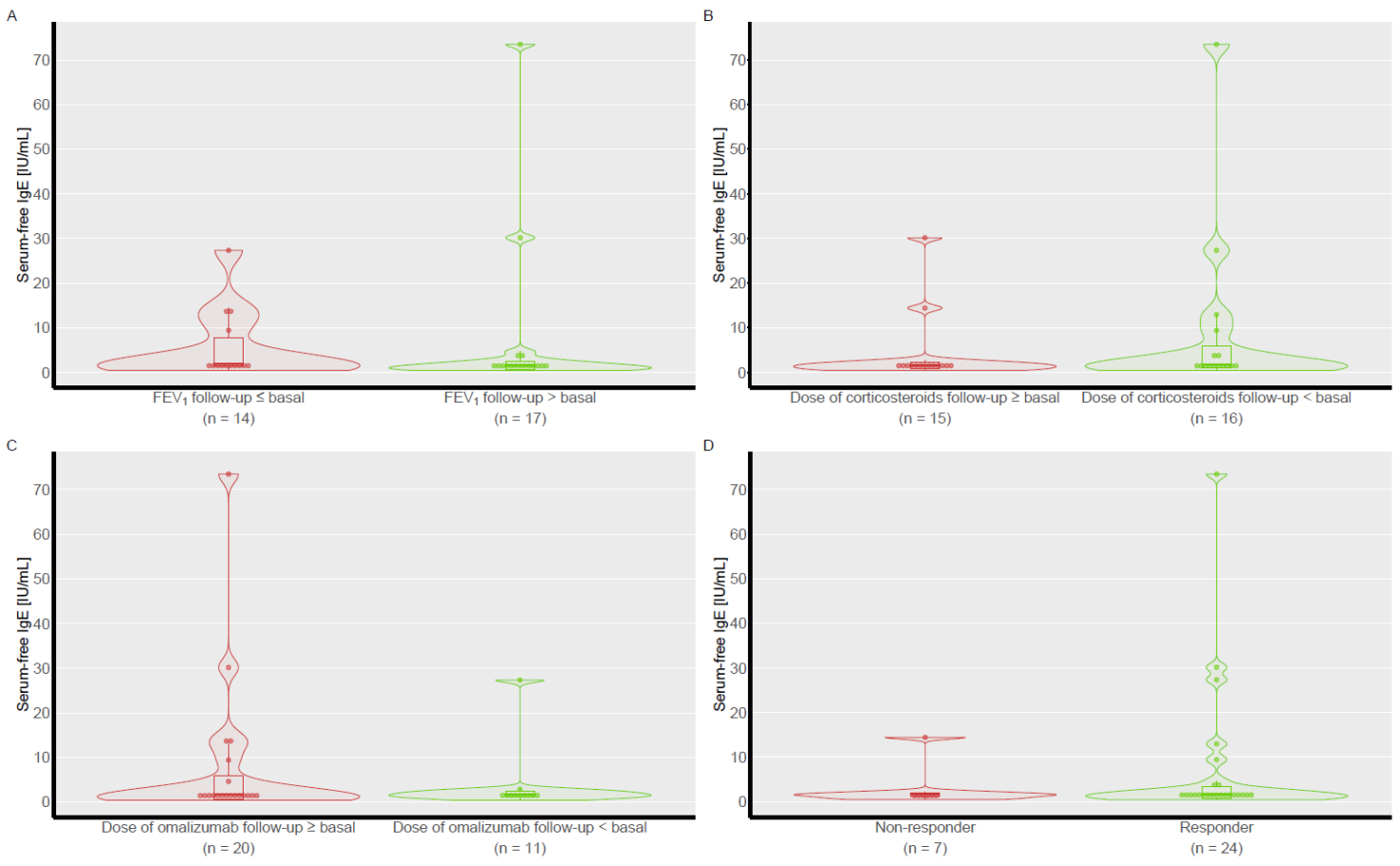
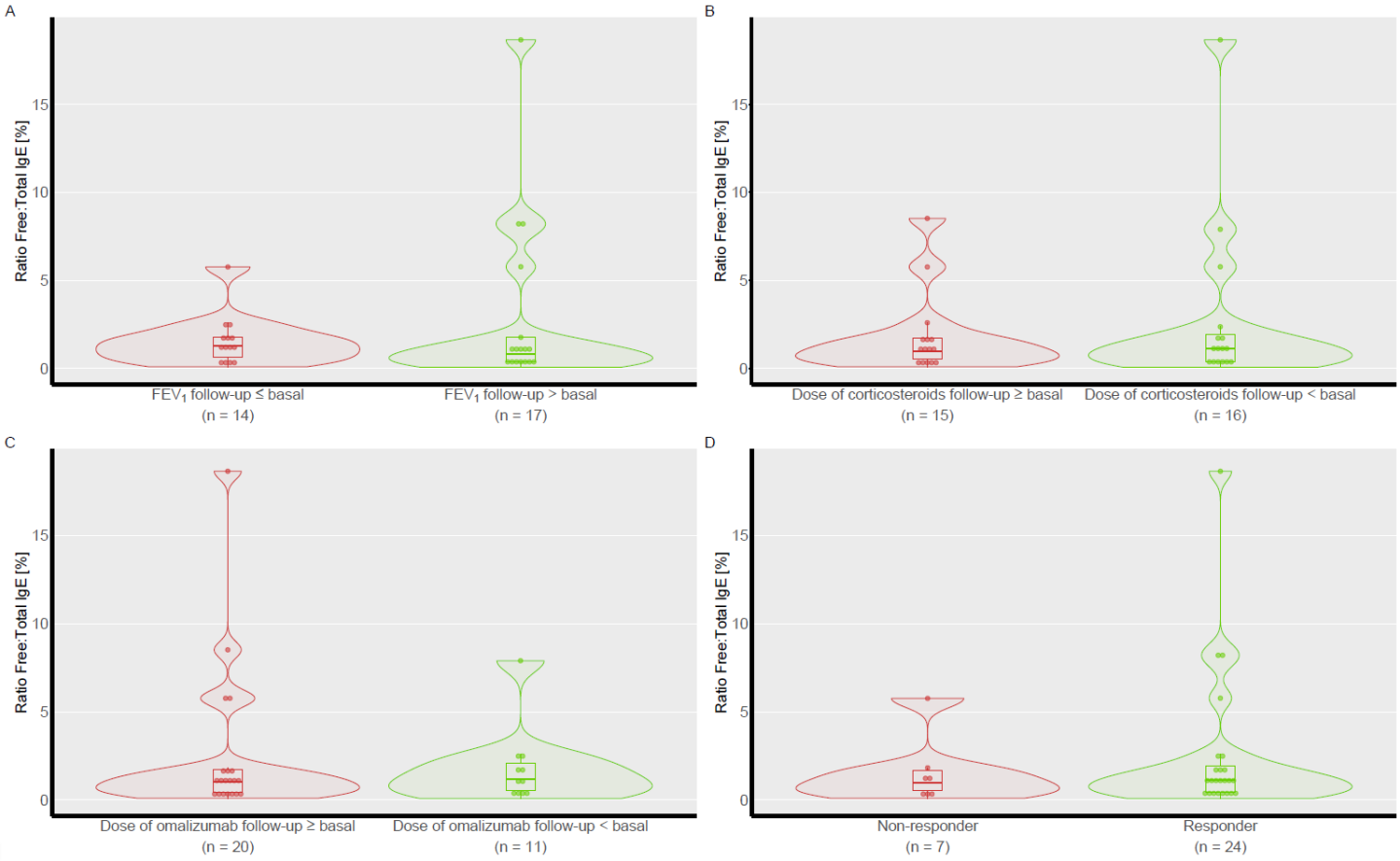


Figure 9: The concentration of the ratio free IgE/Total IgE is shown in figures A-D.



5.4. Analysis of Predictive capacity of IgE on treatment response.

Free IgE (IU/mL): The area under the curve (AUC) (95% CI) of free-IgE for treatment response was 0.45 (0.227; 0.678). The number of observations available for this analysis was 31.

Ratio Free IgE/Total IgE: The area under the curve (AUC) (95% CI) IgE for treatment response was 0.47 (0.223, 0.717). The number of observations available for this analysis was 31.

The free blood IgE concentration as well as the ratio free IgE/total IgE after six months of treatment with omalizumab failed to be a predictor of clinical response to omalizumab.

5.5. Database

The data base used for this study can be found in Appendix 10.9.

6. DISCUSSION

In this study, a high percentage of patients treated with omalizumab presented a notable clinical response. The parameters used to measure this response were objective (reduction of OCS and omalizumab doses, improvement on pulmonary function test or a composite index including all three parameters). Almost 80% of treated patients met criteria to be considered responders. Response occurred when 95% of circulating IgE were blocked. As expected, blood IgE notably increased.
Generally speaking, the increase in total IgE levels can be explained by the prolongation of the half-life of IgE (2–3 days) by binding to omalizumab, which has an IgG1 structure (with a half-life of 23-26 days). Our results show that there is a group of patients who may benefit from omalizumab reduction/withdrawal [53]. Finally, determination of free IgE six months after initiation of treatment with omalizumab did not allow discrimination between responders and non-responders.

We used different objective criteria and a composite index to study the response to an anti-IgE drug and found that the percentage of responders ranged between 45 and 78% of the patients depending on the criteria used. The dose of omalizumab also decreased in the group as a whole confirming the utility of the OMADORE protocol [53].
When free IgE and the ratio free IgE/total IgE were evaluated, we found that 97-98% of them were blocked. This effect occurred in all for groups and the comparison between groups did not show statistically significance.

IgE and its high-affinity receptor (FcεRI) play a pivotal role in the pathophysiology of asthma and other allergic diseases. Within minutes of exposure to the allergen, FcεRI+ mast cells bearing IgE directed against the relevant allergen become activated and release a variety of mediators, chemotactic factors, and cytokines. Omalizumab, an anti-IgE monoclonal antibody, was reported to be effective in reducing systemic side effects of subcutaneous immunotherapy for inhaled allergen in pollen-induced allergic rhinitis, mild–moderate allergic asthma, and venom allergy [67]. Omalizumab also proved effective for pre-treatment and concurrent treatment of venom immunotherapy when anaphylaxis had occurred during initial

immunotherapy [67]. As for its effect in acute allergic reactions (especially anaphylaxis), one would expect the IgE blockade to have an immediate effect on allergic asthma as well, but this is not the case; omalizumab does not play a central role in the management of acute clinical asthma allergic exacerbation.

It should be noted that IgE must bind to its surface receptors, and therefore the total number as well as the percentage of receptors bound to IgE molecules play as important role as IgE alone. Dendritic cells in peripheral blood (the stage in the dendritic cell life cycle that immediately precedes recruitment into the lung) did not show an increased expression of FcεRI in atopic asthmatic subjects compared to healthy, non-atopic subjects. These similar levels of expression of FcεRI in peripheral blood dendritic cells from healthy and asthmatic subjects suggest that the local environment in the airway is responsible for the upregulation of surface FcεRI on airway dendritic cells in asthma. The results also suggest that the functional ability of FcεRI to bind IgE is controlled differentially in the atopic state [10]. Once dendritic cells enter the lung, local microenvironmental factors may be responsible for the greater expression of FcεRI reported for these cells in the asthmatic airway [10].

This may be caused by the effect of thymic stromal lymphopoietin (TSLP), an alarmin released by the damaged bronchial epithelium that has been shown to regulate the activity of dendritic cells [1].

The expression of FcεRI on other cells present at allergic reaction sites, such as eosinophils, suggests that its function goes beyond its role in type I hypersensitivity [10].

The increased receptor expression may be due to the inhaled corticosteroid treatment that the subjects with more severe disease were receiving. Corticosteroids may cause an increase in FcεRI expression on dendritic cells by changing the differentiated state of the cell [73-75]; the maximum expression of FcεRI is found in immature dendritic cells.

Omalizumab (Xolair®, Novartis) is a humanized monoclonal antibody that binds selectively to IgE and prevents it from binding to the FcεRI receptor in basophils and mast cells, thereby reducing the amount of free IgE available to trigger the allergic cascade [76]. By blocking IgE from binding to FcεRI receptors, omalizumab achieves a 97% reduction in the expression of these receptors on the surface of

mast cells and basophils [76]. Moreover, because of the binding of omalizumab to free IgE, blood IgE levels decrease by between 96% and 99%, and as a result of the depletion of free IgE, the plasma membrane FcεRI receptors of basophils are transferred to the cytoplasm and are not resynthesized. This effect, which may contribute to explaining the pharmacodynamic effect of omalizumab, does not occur immediately [77].
Omalizumab binds to circulating free IgE and thereby inhibits binding of IgE to FcεRI. Since it does not bind IgE on the cell surface, it does not directly affect mast cells and basophils. The drug has shown to have an effect in the inhibition of IgE synthesis in peripheral blood mononuclear cells, which was observed not only at the level of protein synthesis but also in the expression of coding IgE mRNA [78]. Finally, by binding to the domain Cε3 of IgE expressed by B cells (IgE which have never been released to the blood, but which are anchored to the cell membrane through a M'domain and not bound to the FcεRI [76]) omalizumab favours the apoptosis of B cells.

Omalizumab has been shown to have some effect on eosinophilic inflammation [70], that is, by regulating the number of eosinophils in sputum as well in bronchial mucosa. This effect may also be delayed.
Last but not least, the calculation of the drug dose may be inaccurate. The dose is calculated on the basis of the patient's weight and plasma IgE concentration. When the sensitized patient undergoes massive exposure to the allergen, IgE production may increase and the concentration of omalizumab in the blood may decrease as days pass and so the dose received by the patient at that time may be inadequate.

As a result, omalizumab may block the acute release of some mediators related to anaphylaxis, but in asthma there are many other pathways.

We can conclude that a high percentage of patients treated with omalizumab have a good clinical response (around 80%). The high rate of the IgE blockade around 99% obviously counteracts the situations triggered by the immediate effect of IgE release. The treatment causes an apparent increase in total IgE, but 98% are inactive since they are bound to omalizumab. In asthma the situation is different; apart from the immediate beneficial effect of the IgE blockade, many effects occur

later, which may explain why the measurement of free IgE after six months of treatment does not distinguish between long-term responders and non-responders. Thus, we can conclude that the determination of free IgE does not allow discrimination between responders and non-responders; therefore, free IgE is not a good biomarker for guiding modifications in the omalizumab dose designed to improve patients' long-term clinical response.

7. CONCLUSIONS

From our study we can conclude:

1. The percentage of responding patients were the following:
    - according to FEV1: 45.2%
    - according to omalizumab dose: 64.5%
    - according to oral corticosteroid dose: 48.4%
    - according to the composite index combining the three criteria: 77.4%

2. The total blood IgE increased 2.7 –fold at months six to decrease to at month 30 to decrease to 1.8 times at month thirty.

3. The mean free IgE concentration in responder patients did not show statistically significance differences.

4. The percentage of free IgE after six months of treatment with omalizumab was 2.33%. The free IgE concentration after six months of omalizumab, was not a predictor of response to treatment.

8. CLINICAL IMPLICATIONS / LINES OF FUTURE RESEARCH

8.1. Clinical implications

Although potentially the measurement of free IgE concentration in blood could be considered useful in discriminating between responders and non-responders, evidence shows that it is not a useful and reliable biomarker.

8.2. Lines of future research

The hypothesis that the measurement of free IgE can be a good biomarker seems to have been completed.
Perhaps an attempt could be made to determine changes in the allergen-specific IgE involved.
Since it has been observed that IgE production decreases with treatment time, it will be necessary to investigate in a larger population whether the timing of the inflection of IgE production can be a useful biomarker.

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10. APPENDIX

10.1. Appendix 1: Publications

.- Domingo C, Monserrate DR, Sogo A, Mirapeix RM. The Incredible Adventure of Omalizumab. Int J Mol Sci. 2024 Mar 6;25(5):3056.
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Int J Mol Sci: IF: 5.6
Q1 Biochemistry & Molecular Biology
Q1 Inorganic Chemistry

.- Free-IgE as a predictor factor of responsiveness to omalizumab in oral corticosteroid-dependent asthma patients.
(Submitted)

International Journal of
Molecular Sciences

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Review

The Incredible Adventure of Omalizumab

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Abstract: The basis of our current understanding of allergies begins with the discovery of IgE in the mid-1960s. The whole theory of the physiology and pathophysiology of allergic diseases, including rhinitis and asthma, dates from that period. Among the key regions of IgE identified were the FAB (fragment antigen binding) portion that has the ability to capture allergens, and the Cε3 domain, through which IgE binds to its membrane receptor. It was then postulated that blocking IgE at the level of the Cε3 domain would prevent it from binding to its receptor and thus set in motion the allergic cascade. This was the beginning of the development of omalizumab, a monoclonal antibody with an anti-IgE effect. In this article, we review the pathophysiology of allergic disease and trace the clinical development of omalizumab. We also review the benefits of omalizumab treatment that are apparently unrelated to allergies, such as its effect on immunity and bronchial remodeling.

Keywords: IgE; omalizumab; pivotal studies; real-life studies; safety; immunity; remodeling

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1. Introduction

In the early 20th century, asthma was classified as either extrinsic and intrinsic. The extrinsic form was identified with allergic asthma. In 1967, a new protein, immunoglobulin E (IgE), was discovered independently by Kimishige and Teruko Ishizaka in Denver, Colorado and by Bennich and Johansson in Uppsala, Sweden, and it was shown to cause allergic processes. The discovery of IgE, and later of specific IgE (IgE developed by the individual against a specific allergen), paved the way for the development of allergy vaccines during the last 25 years of the 20th century. Knowledge of the pathophysiology of asthma (especially early allergic asthma) expanded, disease markers were defined, and asthma phenotypes were described. All of this was linked to the development of new drugs known as biologics (so called because they were originally obtained from live Chinese hamster cells) or monoclonal antibodies (mAbs) [1]. Thanks to the knowledge obtained from the administration of immunotherapy for allergy, IgE took on special importance at the beginning of this process [2]. It was seen that the allergic process began with the activation of dendritic cells or antigen-presenting cells (APCs). The presence of allergens, antigens that favour the production and release of IgE to the medium by plasma cells, promotes the activation of the Th2 pathway, a pathway that requires the differentiation of Th0 lymphocytes (naïve T lymphocytes) into Th2 lymphocytes, and which is able to generate IgE against each allergen to which it is sensitized. This is why this process was called adaptive immunity (i.e., the production of the type of antibody "adapts" to the different allergens with which the individual has been in contact) [3]. As the cell initiating the reaction was the Th2 lymphocyte, the pathway was also called the Th2 pathway. The first monoclonal antibody to be marketed for bronchial asthma was omalizumab, a free IgE blocker [3,4]. Allergen-sensitized IgE-producing patients with clinical symptoms as a consequence of allergen exposure were termed the allergic phenotype.

Subsequently, it was learned that during this Th2 process other molecules known as interleukins (IL5, IL4, IL13) are released into the environment [5]. It has been confirmed that the presence of these interleukins favours, respectively, the synthesis, maturation, and recruitment of eosinophils, the activation of the Th2 pathway, and the blocking of the expression of vascular cell adhesion molecules (VCAM-1s), and finally the activation of the enzyme that regulates the release of the exhaled fraction of nitric oxide (FeNO), nitric oxide synthase [5].

More recently, it has been observed that apart from this adaptive pathway, the activation of the innate immunity also occurs, which is produced by other molecules: thymic stromal lymphopoietin (TSLP), IL33, and IL25 [1,5]. It was observed that these mediators appear as a result of damage to the bronchial ciliated epithelium, which releases them into the environment [1]. Since they represent an alarm signal warning of epithelial damage, they were named alarmins. This pathway is activated by the effects of different antigens (including allergens which would act in this case by inflammatory and non-allergenic means), and by pollution, tobacco, viruses and bacteria, etc., which damage the bronchial epithelium. This pathway always responds in the same way, thus differentiating it from the adaptive pathway in which the production of specific IgE against each allergen to which the individual is sensitized occurs. Because they are mediated by the innate lymphoid cells type 2 (ILC2), and as an analogy with the allergic cascade which was called Th2 due to the participation of Th2 lymphocytes, the innate and adaptive pathway as a whole were called T2; hence the classification of asthma into T2 and non-T2 [5].

These alarmins directly activate the cells of innate immunity, the ILC2 and the natural killer T cells (NKT cells). These alarmins, especially TSLP, exert control over the activity of antigen-presenting cells. T2 asthma (and perhaps non-T2 asthma) then becomes an epithelium-driven disease [1]. As mentioned above, anti-alarmin monoclonal antibodies are currently being developed [6]. When we administer a mAb, we are modifying the phenotype of the individual, and this causes the organism to try to maintain the lost balance by activating other pathways. We will now describe the scientific and clinical development of the first monoclonal antibody that was marketed two decades ago.

2. Structure of IgE

IgE has the structure shown in Figure 1. It has two light chains and two heavy chains. Of special relevance is the Cε3 domain, since it is the region through which IgE will bind to its cell surface receptor and is therefore the domain to be pharmacologically blocked. The Cε3 domain is the fraction of the IgE molecule that binds to membrane receptors, and it is the domain to which omalizumab (the anti-IgE antibody) will bind. The key epitope is therefore the Cε3 domain of human IgE [2,3].

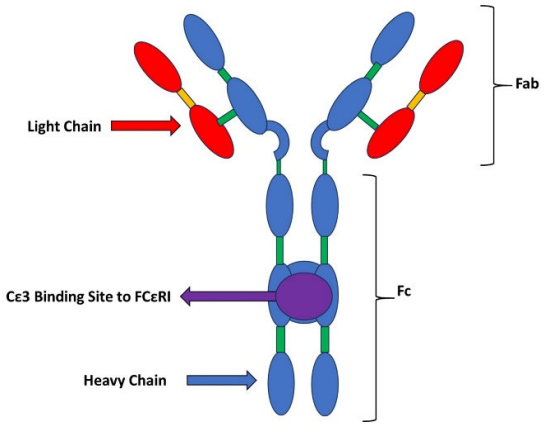
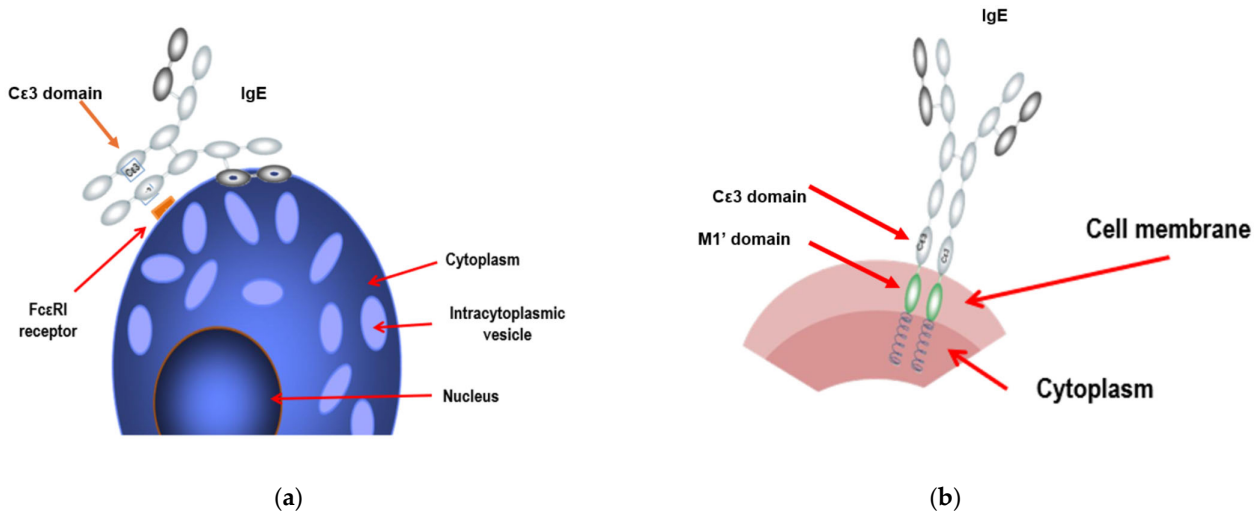


Figure 1. Structure of IgE (modified from [2]). The Cε3 domain is the fraction of the IgE molecule that binds to membrane receptors. The key epitope is the Cε3 domain of human IgE.

3. Types of IgE

There are two types of IgE: the molecules released into the environment, and those expressed by the cell. In the sensitization process, the cell produces IgE molecules which are released and can be measured in a blood serum test, and these are the ones that will bind to their high- (FcεRI,) and low-affinity (FcεRII) receptors. There is, however, a second type of IgE: the molecules that are not released into the environment and which therefore are not measurable (that is, we cannot determine their presence in a blood test). These are the IgE molecules expressed by the cell. After the first exposure to the allergen and the initiation of the sensitization process, the individual's B cells will now express IgE on their surface rather than IgG (these IgE molecules being very similar to the ones that they will produce and release). Unlike the IgE released into the environment, the B cells produce IgE that have an M1′ domain that allows them to anchor to the cell membrane, but not by binding to the FcεRI receptor. At this time, the B cells are already clearly differentiated (Figure 2a,b).



(**a**) (**b**)

Figure 2. Types of IgE. There are two types: those secreted into the medium that bind to the cell receptor through the Cε3 domain (**a**) and the non-secreted (or membrane) IgE molecules, which are synthesized and expressed by the cell at the level of its cell membrane (**b**).

One might think that these cell-expressed IgE molecules do not play any role in the allergic process. However, this is not the case. Allergens that continue to penetrate the organism can follow three pathways: keeping the allergic cascade active by stimulating the process from the dendritic cells; favouring mast cell degranulation as each allergen molecule is captured by two IgE molecules (a cross-linking phenomenon already described above); or stimulating the Th2 pathway by interacting with these membrane IgE molecules. From the therapeutic point of view, although the basic aspect is omalizumab's blockade of the Cε3 domain of the IgE secreted into the medium before binding to receptors, the drug can also bind to the Cε3 domain of the IgE expressed by B cells since, as we have said, they are anchored to the cell surface by the M1′ domain, and therefore the Cε3 domain is free. By binding to this membrane IgE, omalizumab provokes apoptosis of these cells [3].

4. Pathogenesis of the Allergic Reaction

When an individual is first exposed to an antigen, dendritic cells (macrophages located in the epithelium of the body) internalize it, process it, and present it to a T-lymphocyte through the major histocompatibility complex type II. In this process, the naïve T lymphocyte can become a T-helper 2 (Th2) or a T-helper 1 (Th1) lymphocyte. The relative amount of each type depends on both the antigen and the host (Figure 1) [2].

When the antigen is an allergen, the lymphocyte differentiates into a Th2 cell capable of producing IL-4, which in turn promotes IgE synthesis by B cells. In addition to regulating

IgE, IL-4 promotes IL-13 production in mast cells. In their membranes, mast cells contain the high-affinity receptor for IgE (FcεRI). When IgE binds to this receptor, it is ready to block the allergen to which it is sensitized. Up to this point (the sensitization phase), no clinical symptoms have appeared. When two or more IgE molecules that have bound to their receptor recognize the same allergen, they cause the cross-linking effect in the receptors, a phenomenon that triggers a series of biochemical signalling reactions culminating in mast cell degranulation [2–4] (Figure 3).

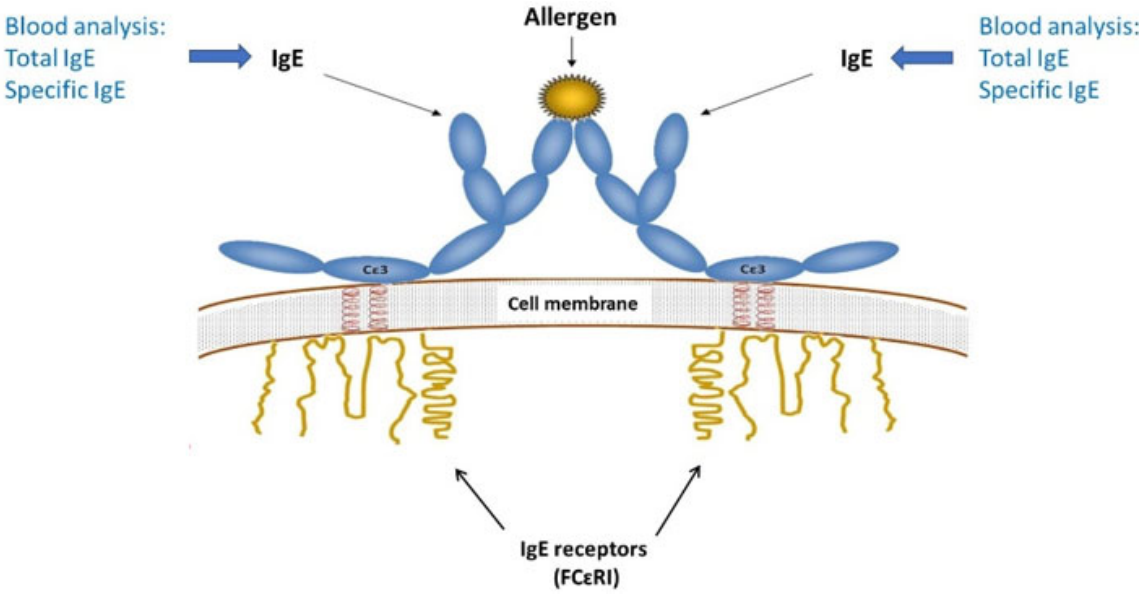


Figure 3. Acute allergic reaction: cross-linking phenomenon (taken from [5]). The individual is sensitized, produces IgE against the allergen to which s/he is sensitized, and these IgE molecules bind to their membrane receptors on mast cells and basophils. When a new allergen appears, two IgE molecules block the allergen, leading to changes in the intracellular component of the IgE receptor. This will cause mediator-loaded vesicles (in this case histamine) to be released into the environment.

In the acute allergic reaction phase, the immediate mediators are released. This phase lasts approximately one hour. Subsequently, a second phase may occur after 4–8 h of exposure to the allergen. The chemotactic factors, IL-5, IL-3, IL-13, and cell growth factors released in the immediate inflammation increase eosinophil recruitment. Eosinophils release IL-5, which in turn perpetuates inflammation (the late reaction phase). This can lead to chronic inflammation in cases of continued exposure to the allergen. Occasionally, if the amount of IgE, eosinophils, and other mediators is very high, this process can persist without the need for an allergenic stimulus (chronic phase) [3].

5. Importance of Immunoglobulin E

In addition to the role described above, IgE collaborates in other aspects of the allergic reaction that are key elements in the pathophysiology of asthma. As we noted above, IgE binds to its high-affinity receptors, FcεRI receptors, on the surfaces of mast cells and basophils, through the Cε3 domain of its Fc fragment. The correlation between FcεRI expression on basophils and serum IgE levels is well established [6]. IgE itself [7] appears to up-regulate FcεRI expression in human basophils, probably by interacting with FcεRI. Recent data have suggested that IgE has some additional immunobiological effects. This molecule may promote mast cell survival through autocrine production of IL-6 [8]. IgE binds to dendritic cells and enhances allergen uptake and presentation to T cells [9]. Dendritic cells from patients with mild atopic asthma have been reported to bind significantly more IgE than cells taken from healthy individuals [10], and FcεRI receptors

are known to be up-regulated on dendritic cells (as well as on eosinophils, mast cells, and macrophages) in patients with seasonal allergic rhinitis [11].

6. Omalizumab

The most important step in the production of a monoclonal antibody is the selection of the target. In the case of anti-IgE therapy, the goal is to obtain a specific monoclonal antibody against a key epitope of the IgE molecule. Omalizumab, known in early trials as rhu Mab-E25, is a humanized murine monoclonal antibody that recognizes the Cε3 domain of human IgE, the part of the molecule that binds to mast cell and basophil receptors. Once bound to these cell receptors, IgE undergoes a spatial transformation that favours allergen recognition. This spatial transformation also affects the Cε3 domain and renders it unrecognizable to omalizumab. As a result, omalizumab binds to free IgE but not to IgE bound to cellular receptors [12].

6.1. Pharmacological Effects of Omalizumab

Initially, it was observed that omalizumab administration produces a rapid and substantial reduction in free serum IgE, which decreases by 99% within 2 h of administration. It also induces the down-regulation of FcεRI in basophils, dendritic cells, and monocytes within 7 days. At 3 months, the amount of FcεRI receptors on basophils decreases by up to 93% [13,14]. Therefore, the effect of omalizumab is to reduce both the amount of free serum IgE and the expression of FcεRI on mast cells and basophils. In addition, the decreased expression of FcεRI on dendritic cells may reduce allergen processing and presentation [15], and, consequently, may lead to reduced lymphocyte activation and decreased cytokine production from Th2 lymphocytes. Finally, omalizumab decreases serum, tissue, and sputum eosinophilia. This whole process is summarized in Figure 4.

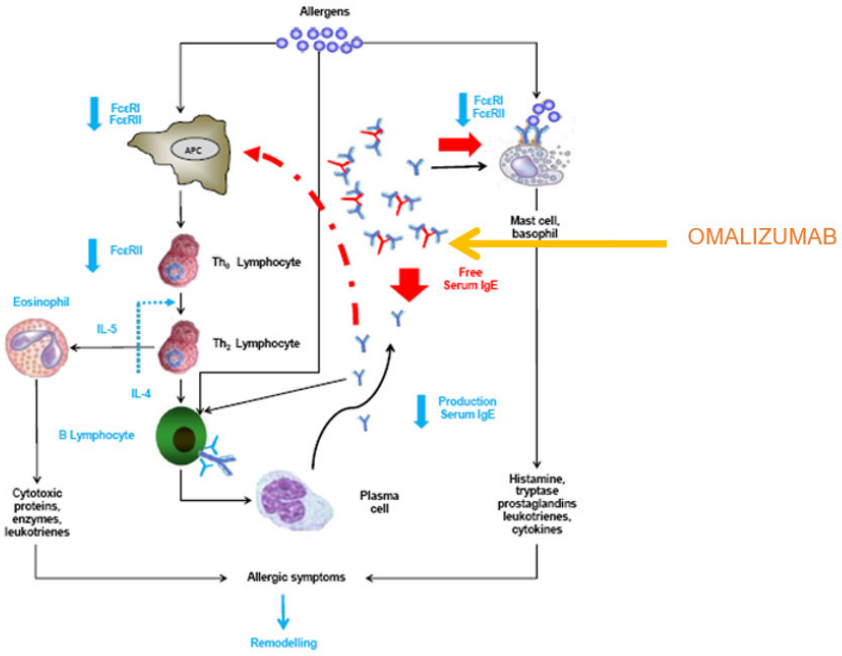


Figure 4. Effects of omalizumab. The steps of the allergic process are shown in black,. The steps blocked by the direct immunoglobulin E (IgE) blocking effect of omalizumab are shown in red. Blue indicates indirect immunomodulation mediated by the action of omalizumab, which causes the down-regulation of the cellular expression of FcεRI, and of FcεRII at different levels, the secretion of interleukin IL-4 and IL-5, and lowers eosinophil and B-lymphocyte levels, as well as IgE production. APC: antigen-presenting cell (modifed from [3], Domingo, C. *Drugs* **2014**, *74*, 521–533).

Subsequently, it was reported that in addition to this direct effect, omalizumab has an immunomodulatory effect, which is shown below:

- Evident reduction of FcεRI expression in mast cells [16].
- Evident reduction of FcεRI expression in basophils [17].
- Decrease in histamine release by basophils [18].
- Reduction in basophils' FcεRI-mediated capacity to release Th2 cytokines [19].
- Decrease in the number of dendritic cells (statistically significant in the case of myeloid dendritic cells (mDCs) and numerical in the case of plasmacytoid dendritic cells (pDCs)) [20].
- Decrease in the number of high-affinity IgE receptors in both pDCs and mDCs in patients with cat allergies [21].
- Decreased dendritic cell-dependent T cell proliferation in co-cultures stimulated with cat allergens [21].
- Significant decrease in the ability of mononuclear cells in culture to release IL-5 [22].

6.2. Clinical Development

Despite being the first biologic drug introduced, the development of omalizumab was very well programmed. In addition to its pharmacokinetic effects, the study of its pharmacodynamic effects was very thorough. The pivotal studies and the most important of the many real-life studies are described below.

6.2.1. Studies Leading to the Development of Omalizumab

Pivotal Studies

Table 1 summarizes the most relevant data from pivotal studies focusing on patients with moderate/severe asthma. They show a notable and always significant reduction in exacerbations compared to placebo, and also demonstrate the drug's safety. One of them also reports a marked reduction in inhaled corticosteroid use.

Table 1. Summary of pivotal studies.

Author	Year	Study	Asthma Severity	N° of Patients	Efficacy Variable	Results	Duration (Weeks)
Busse [23]	2001	008	Severe	525	Exacerbations	↓ 48%	28
Solèr [24]	2001	009	Moderate–Severe	546	Exacerbations	↓ 58–52%	52
Holgate [25]	2004	011	Severe	246	ICS saving	74% of patients ↓ FTC ≥ 50%	32Yes, this
Vignola [26]	2004	SOLAR	Moderate–Severe	405	Exacerbations AQLQ	↓ 38%	28
Ayres [27]	2004	ETOPA	Moderate–Severe	312	Exacerbations/ worsening of asthma	↓ 61%	52
Bousquet [28]	2004	ALTO	Moderate–Severe	1899	Safety		24
Humbert [29]	2005	INNOVATE	Severe	419	Exacerbations	↓ 50%	28

ICS: inhaled corticosteroids. FTC: fluticasone.

Undoubtedly, the most significant study is the INNOVATE study, which reported the following:

- A 50% reduction in severe exacerbations.
- A 44% reduction in emergency room visits.
- An improvement in the quality of life assessed by the AQLQ (asthma quality of life questionnaire), both in the overall score and in the various dimensions. The overall difference was statistically significant compared to placebo, although it did not reach the clinically relevant value of 0.5.

Real-Life Studies

Two real-life studies of omalizumab, one by Braunstahl (eXpeRience) [30] and one by Korn [31], stand out. The eXpeRience study was an international, open-label, single treatment arm, 2-year study involving 14 countries in Europe, the US, and Asia, and designed to evaluate the effectiveness of omalizumab. It included 943 patients with uncontrolled allergic asthma. Among the most noteworthy results were the following:

- The limitation in activities of daily living (ADLs) was reduced from 4.4 days per week to 1.3 and 1.2 at one and two years of follow-up, respectively.
- A decrease in the use of rescue medication that ran parallel to the improvement in ADLs. Consumption fell from 4.8 days per week to 1.8 and 1.6 at one and two years of treatment, respectively.
- The average annual days off work fell from 26.4 before the start of treatment with omalizumab to 3.5 and 1.0 days after one and two years of treatment with omalizumab, respectively.
- An increase in the percentage of patients without clinically relevant exacerbations (either severe or non-severe).

6.2.2. Specific Aspects of the Development of Omalizumab

Fall in Exacerbations

The INNOVATE study [29] showed that the rate of clinically significant exacerbations (the primary efficacy endpoint), adjusted for an observed imbalance in exacerbation history, was 0.68 with omalizumab and 0.91 with placebo, representing a 26% reduction during the 28-week treatment phase. Without adjustment, a similar magnitude of effect (a 19% reduction) was observed, although it did not reach statistical significance. The CHOC study (Clinical and Histological impact of treatment with Omalizumab in severe allergic oral Corticosteroid dependent allergic asthma patients) [32] reported a 54% reduction in total exacerbations. For severe exacerbations, the INNOVATE study [29] showed an annualized reduction of 50%. In the CHOC study [32], none of the patients treated with omalizumab had severe exacerbations during follow-up, and exacerbation duration was reduced by half.

Two real-life studies involving oral corticosteroid (OC)-dependent patients (the eXpeRience registry [30], with 28.1% of patients receiving OC, and the Xpertise trial [31], with 46%) showed reductions in exacerbations of more than 80%.

In addition to exacerbations, some studies have measured emergency department visits or hospitalizations. The INNOVATE study [29], in which OC-dependent patients represented 22% of the sample, showed a 44% annual reduction in emergency room visits. In a real-life study, Molimard et al. [33] found a 65% reduction in annual ED visits after treatment with omalizumab. In Germany, in a population of 280 patients, 46% of whom were cortico-dependent, Korn et al. [31] reported an 82% reduction in exacerbations and a 78% reduction in hospitalizations.

Corticosteroid Sparing Capacity

The Cochrane review [34] concluded that treatment with omalizumab was associated with a significant possibility of reducing inhaled corticosteroid doses or of withdrawing them completely. The mean dose reduction was −118 µg beclomethasone dipropionate equivalents. In the subgroup of patients receiving OCs, it was unclear whether this benefit occurred. In a subgroup analysis in an open-label parallel-group study, Siergiejko et al. [35] found that at week 32, 62.7% of patients in the treated group were able to discontinue or reduce OCs compared with 30.4% of controls. The real-life eXpeRience study [30] found a relative reduction of 50% at month 24, and the APEX study, a retrospective study conducted in the UK, found a 34% reduction in the mean total amount of prescribed OCs per year and complete cessation of OC use after 12 months in 48% of patients [36]. In a 2-year prospective observational study, Domingo et al. [37] reported that omalizumab allowed OC withdrawal in 74.2% of patients. Real-life studies are usually understood to obtain better results than randomized clinical trials, but the CHOC study [32] presented results of the

same order as the best real-life studies. In this open randomized study, it was observed that 12 patients (75%) in the omalizumab group and only one (7.7%) in the control group were able to cease OC treatment.

Biomarkers Predicting Response to Omalizumab

The biomarkers that have been evaluated are the exhaled fraction of nitric oxide (FeNO), peripheral blood eosinophils, peripheral blood immunoglobulin E (IgE) concentration, and, in experimental studies, the blood periostin value. An early study by Djukanovic [14] in 45 patients with mild/moderate asthma, who were divided into two groups of 22 (omalizumab) and 23 (placebo), showed at 16 weeks that treatment with omalizumab decreased the number of eosinophils in patient sputum (from 6.6% to 1.7% in the treated group; $p = 0.05$) versus a non-significant decrease in the placebo group (from 8.5% to 7.0%). This decrease was also observed in bronchial biopsy specimens.

The EXTRA study [38] found the patients with the lowest incidence of exacerbations to be those with FeNO values $\geq$ 19.5 ppb, eosinophils $\geq$ 260 µL, and periostin $\geq$ 50 ng/mL.

Eosinophil rates may be elevated in allergic patients without the patient exhibiting an eoosinophilic phenotype. There is some controversy as to whether this biomarker can condition the response to treatment with omalizumab. A study by Casale et al. [39] also showed that the baseline eosinophil level, as well as other clinical markers, predicted response to omalizumab. Patients with a history of frequent ED visits, hospitalizations, FEV1 (%) values < 65%, beclomethasone dipropionate doses of $\geq$600 µg, and who use long-acting beta-agonists (LABAs) are the best responders to omalizumab. The STELLAIR retrospective study [40], conducted in France, included 872 patients (723 adults and 149 non-adults aged 6–17 years) with severe allergic asthma who were treated with omalizumab by 78 physicians. The mean eosinophil count was $\geq$300 cells-µL-1 in 52.1% of the adults and in 73.8% of the children/adolescents. The percentage of responders did not vary in the subgroups established according to the baseline eosinophil value, leading the authors to suggest that the eosinophil level is not a good predictor of response to omalizumab.

Finally, it has been speculated that omalizumab may have a long-term effect on IgE synthesis. Lowe and Renard [41] obtained data on omalizumab and free and total IgE from an epidemiological study and from six randomized, double-blind, placebo-controlled trials in patients with allergic asthma. IgE production and clearance were modelled, and it was concluded that after five years of treatment, IgE production decreases. In a study in which free IgE and total IgE (free + blocked with omalizumab) were measured, Domingo et al. [42] observed a decrease in IgE production. This result appeared to justify the discontinuation of treatment after five years, but this biological observation did not correspond to the clinical findings, and cannot therefore be used as a criterion for stopping treatment.

6.3. Long-Term Tolerance

When a new drug is introduced, one of the key aspects is its safety. The EXCEL study [43,44], conducted at the request of the FDA, was a post-marketing study that included 4972 patients treated with omalizumab and 2867 patients who were not treated. It demonstrated the safety of the drug, but raised doubts about the incidence of neoplasms, which appeared to be higher in the treated group. The increased risk was attributed to the fact that the treated group was followed for a longer time. Subsequently, a study by Long et al. [45] showed that omalizumab treatment does not increase the incidence of malignancies. A recent retrospective study in 45 patients with a mean follow-up of 10.6 $\pm$ 1.2 years [46] has also shown the effectiveness and safety of the drug.

6.4. Withdrawal of Treatment

An early study showed that after omalizumab withdrawal, symptoms reappear and are accompanied by an increase in free IgE [47]. Subsequently, Molimard et al. [48] observed a loss of asthma control in 55.7% of patients 13 months after treatment withdrawal. After six years of treatment, Kupryś-Lipińska and Kuna [49] observed that 9/11 (81.8%)

presented exacerbations within five months of treatment withdrawal. A study by Nopp et al. [50] in a population of cat epithelium allergic individuals demonstrated that three years after withdrawal from a six-year treatment programme with omalizumab, there was no loss of respiratory function. In the XPORT study [51], a randomized study with two treatment groups (a minimum of five years with omalizumab versus placebo) showed that patients who continued with omalizumab had better asthma control during the 52 weeks of the study. Vennera et al. [52] observed that despite five years of treatment with omalizumab, the number of patients with severe exacerbations increased over time, with 39% of patients presenting severe exacerbations four years after discontinuation of treatment. The OMADORE study [53] is the only study that has proved able to identify patients in whom omalizumab can be safely withdrawn. Among the patients who met the clinical stability criteria and whose FEV1% did not deteriorate after 18–24 months of treatment, those who tolerated the decrease did so between 18–40 months after starting treatment; they tended to be younger and have better GETE, improved FEV1% after the first dose of omalizumab, reduced oral corticosteroid use, and FeNO values < 50 ppb. With this protocol, omalizumab could be withdrawn in approximately one third of patients, without severe exacerbations occurring during the following 30 months. More recently, in a retrospective study in France based on information from a national health service data registry, 16,750 adults and 2452 children (age $\geq$ 6 years) were identified with median periods of omalizumab treatment before withdrawal of 51.2 and 53.7 months, respectively. Among the adults who discontinued omalizumab when their asthma was controlled, 70%, 39%, and 24% remained controlled and did not resume omalizumab treatment one, two, and three years after discontinuation, respectively [54].

6.5. Particular Effects of Omalizumab

In addition to the descriptions above, numerous studies have revealed other unexpected effects of the drug.

6.5.1. Omalizumab and Remodelling

Information on remodelling and biologic treatments in patients with severe asthma is limited and often indirect. Omalizumab has been shown to decrease endothelin-1 clearance in exhaled air [55], reduce bronchial wall thickness, and increase the bronchial endoluminal area [56]. Two ex vivo studies have shown that the presence of IgE induces extracellular matrix and collagen deposition and antagonizing IgE reverses these effects [57,58]. The only study to demonstrate the reversibility of remodelling in the ciliated epithelium (including the reappearance of cilia) and reductions in intracellular spaces and in the thickness of the basement membrane is the CHOC study [32].

6.5.2. Omalizumab and Infections

Among the factors that predispose patients to the triggering of asthma exacerbations are respiratory infections of viral origin, which lead to peaks of exacerbations throughout the year. This is clearly evidenced in the study by Johnston et al. [59].

The possibility that there might be a relationship between the presence of IgE molecules and their binding to their high-affinity receptors and lung infections was raised when a decrease in interferon production was observed in patients with asthma infected by the influenza virus; in this situation, there was an inverse relationship between IgE blood concentration and interferon production [60]. It was suggested that the production of interferon by plasmacytoid dendritic cells might be down-regulated due to the binding of free IgE molecules to their high-affinity receptors upon the activation of a cascade that blocks the order sent from toll-like receptors stimulated by the presence of viral genetic material (Figure 5).

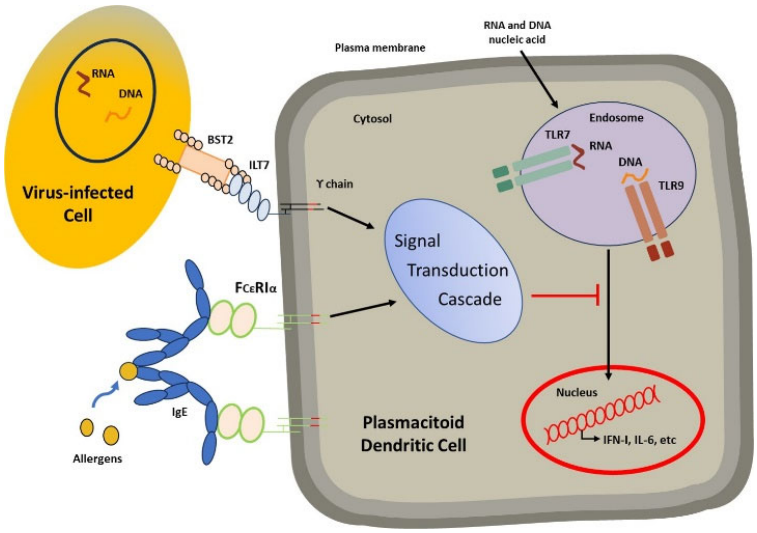


Figure 5. Modified from Lynch et al. [61]. The figure shows how IgE molecules bind to their receptors and are ready for the cross-linking phenomenon to occur in the presence of allergens. This will activate the cascade that blocks the command sent from the toll-like receptors for the nucleus to synthesize interferon.

If all this is true, it makes sense to examine whether blocking IgE might stop the cross-linking phenomenon, and whether interferon production in the presence of viral genetic material would therefore remain intact. This possibility was clinically confirmed by the ICATA study [62], which showed that treatment with omalizumab improves the control of allergic asthma, prevents seasonal exacerbations, and reduces the consumption of inhaled corticosteroids.

The PROSE study confirmed that the addition of omalizumab 4–6 weeks before the start of the school year and maintained for the following four months reduced exacerbations more than in the placebo group and in the group that received a reinforcement of inhaled corticosteroids, since it contributed to restoring the defensive mechanisms [63]. This benefit also seems to extend to asthmatic children with more severe disease [64].

6.6. Omalizumab and Pregnancy

Information on the use of omalizumab during pregnancy is limited. However, the Expect registry [65] collected information from 230 pregnant women (64.9% with severe asthma and 35.1% with moderate asthma) treated with omalizumab from 2006 to 2017 in the US and compared these data with those obtained from a cohort of 1153 women from Quebec (21.2% with severe asthma and 78.8% with moderate asthma) who were not treated with omalizumab, which served as a control. The study concluded that omalizumab can be safely administered to pregnant women, and that it does not increase the risk of malformations in the foetus or the risk of small size for gestational age.

6.7. Indication of Omalizumab

The drug is indicated in patients with severe allergic asthma. Certain factors regarding the initial indication and subsequent modifications should be borne in mind (see Table 2) [3].

It has also been observed that omalizumab is effective in patients with severe allergic asthma who have been sensitized to seasonal allergens [66]; however, this indication does not appear on the technical data sheet. Other exploratory indications include the administration of the drug as a preventive treatment in cases of immunotherapy for venoms [67] or in exercise-induced anaphylaxis [68]. These prescriptions should be made in specialized units.

Table 2. Criteria for indication of omalizumab at the start of marketing and subsequent modifications.

	At Marketing	Post-Marketing Modification
Age (years)	≥12	≥6
Allergy sensitization	Positive skin prick test or in vitro reactivity to at least one perennial aeroallergen	Positive skin prick test or in vitro reactivity to at least one perennial aeroallergen
Baseline immunoglobulin E level	≥30–700 kU/L	≥30–1500 kU/L
Monthly calculated omalizumab dose	≤750 mg	≤1200 mg
Asthma severity	Severe or inadequately controlled asthma	Severe or inadequately controlled asthma
Re-evaluation	After 16 weeks of treatment	After 16 weeks of treatment
Long-term treatment withdrawn	Not specified	Not specified

7. Conclusions

Omalizumab has had an exemplary theoretical and practical development. By blocking IgE, a molecule that is undoubtedly central to the development of allergic reactions, it has led to a better understanding of the Th2 pathway and has contributed to the concept of T2 inflammation. The exemplary development of omalizumab over the past 20 years has enabled shorter development times for other monoclonal antibodies that block molecules such as the interleukins IL5, IL4, and IL13 and the alarmins TSLP, IL33, and IL25.

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10.2. Appendix 2: Informed Consent

FORMULARIO DE CONSENTIMIENTO INFORMADO

Título del estudio: IgE libres como factor predictor de respuesta a omalizumab
.
Promotor del estudio: Dr. Christian Domingo
Código del estudio: FIS código CDR-OMA-2012-01/PI11/02303

Yo, (nombre y apellidos) .....

He leído la hoja de información sobre el estudio

• He podido hacer preguntas sobre el estudio.
• He recibido suficiente información sobre el estudio.
• He hablado con el doctor .....

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:
• Cuando quiera
• Sin tener que dar explicaciones
• Sin que esto repercuta en mis cuidados médicos.

Entiendo que al acceder a participar en este estudio, consiento en la recogida, tratamiento, cesión y transferencia (si procede) de mis datos personales, con respeto al anonimato, para fines de atención sanitaria y/o investigación médica.
Presto libremente mi conformidad para participar en el estudio y que mis datos puedan ser utilizados con fines de investigación.

Firma del/la participante: .....

Fecha:

_____/_____/_____
Día *Mes* *Año*

Firma del investigador: .....

Fecha: _____/_____/_____
Día *Mes* *Año*
Por favor, recuerde que el formulario ha de ser completado POR EL/LA PARTICIPANTE, de su puño y letra.
El paciente debe recibir una copia de la hoja de información al paciente y consentimiento informado.
Muchas gracias por su colaboración
Dr. Christian Domingo **Página** 1**de** 3

10.3. Appendix 3: Patients' Information Sheet

HOJA DE INFORMACIÓN AL PACIENTE
Título del estudio: IgE libres como factor predictor de respuesta a omalizumab
Promotor del estudio: Dr. Christian Domingo
Código del estudio: FIS código CDR-OMA-2012-01/PI11/02303
Investigador Principal: Dr. Christian Domingo

Por favor, lea atentamente esta hoja de información.
En estos momentos se le está proponiendo su participación en un estudio de investigación español, que ayudará a entender el papel de una molécula que tenemos en nuestro cuerpo (la inmunoglobulina E-IgE).

Propósito y realización del estudio
El PROMOTOR del estudio pretende desarrollar un proyecto de investigación que tiene como objetivo principal profundizar en el conocimiento de la importancia de la concentración de la IgE libre en sangre, después de la administración de Omalizumab, de cara al pronóstico de su enfermedad. Usted continuará tomando el tratamiento prescrito por su médico y este estudio no afectará para nada al control/evolución de su enfermedad.

Como parte del control de su enfermedad, se le practicarán analíticas de rutina, parte de cuya sangre será utilizadas para este estudio. Ello no supone incrementar su tiempo de estancia en el hospital ni incrementar el riesgo del manejo de su enfermedad.

En este estudio está previsto incluir un total de 30-40 pacientes. La participación en este estudio no supone ningún cambio respecto al seguimiento o tratamiento de su enfermedad.

Participación voluntaria
Su participación es totalmente voluntaria. Es usted libre de rechazar colaborar en este estudio, sin que tenga que explicar los motivos que le llevan a tomar esa decisión y sin que se vea afectada su atención médica.
Puede consultar con otras personas antes de tomar una decisión sobre su participación en el estudio.
Usted puede retirarse del estudio en cualquier momento y sin dar explicaciones.
Su nombre e iniciales no aparecerán en ningún documento del estudio. Usted será identificado exclusivamente por un número, para garantizar la confidencialidad de sus datos. El tratamiento, la comunicación y la cesión de los datos de carácter personal se ajustarán a lo dispuesto en la Ley Orgánica de protección de datos de carácter personal 15/1999 de 13 de diciembre. De acuerdo con esta ley, usted puede ejercer el derecho de acceso, modificación, oposición y cancelación de datos, así como obtener información sobre el uso de sus muestras i datos asociados, para lo cual deberá dirigirse a su médico.

Póliza de seguro
Puesto que no se realiza ninguna exploración o prueba que no sean las habituales para el manejo de su enfermedad, el Promotor del estudio no ha concertado ninguna póliza de seguros con ninguna compañía.

Riesgos de participación
Ninguno adicional al manejo habitual de su enfermedad.

Beneficios de participar
El hecho de proporcionar sus datos médicos para este estudio puede no beneficiarle directamente, pero la información obtenida puede ser utilizada para apoyar la evidencia científica del diseño de estudios posteriores.

Compensación
No se percibirá ninguna compensación económica por la participación en este estudio.

Confidencialidad de los datos
El acceso a su información personal quedará restringido a su médico y colaboradores, y si lo requieren para comprobar los datos y procedimientos del estudio, al Comité Ético de Investigación Clínica que ha aprobado el estudio y al promotor del mismo, pero siempre manteniendo la confidencialidad de sus datos según la legislación vigente.

Si acepta participar en el estudio, los datos obtenidos a lo largo del mismo serán tratados de forma confidencial en todo momento y por cualquier persona autorizada a su acceso. Los datos originales serán conservados en el centro del investigador y sólo tendrán acceso los investigadores del estudio, la/s persona/s encargada/s de su monitorización, el Comité Ético de Investigación Clínica y las Autoridades Sanitarias Españolas. Usted será identificado mediante un código de paciente y los datos obtenidos en el presente estudio seguirán las regulaciones españolas sobre el manejo de datos computerizados (L.O. 15/1999, de 13 de Diciembre de Protección de Datos de Carácter Personal).

Es posible que los resultados de este estudio se presenten en publicaciones o comunicaciones en congresos. En ningún caso se le identificará en estas publicaciones.

Debe saber que este estudio ha sido aprobado por un Comité Ético de Investigación Clínica, y se realizará cumpliendo la legislación vigente en España para este tipo de estudios.

Si tiene alguna duda relativa al estudio, por favor consulte a su médico.
Nombre del médico: .Dr. C.Domingo.....
Teléfono de contacto: ..93 723 10 10.....

Se entregará una copia de la hoja de información al paciente y consentimiento informado al paciente.

10.4. Appendix 4: Patients' Information Sheet for sample release

HOJA DE INFORMACIÓN AL PACIENTE PARA CESIÓN DE MUESTRAS

Título del estudio: IgE libres como factor predictor de respuesta a omalizumab
Promotor del estudio: Dr. Christian Domingo
Código del estudio: FIS código CDR-OMA-2012-01/PI11/02303
Investigador Principal: Dr. Christian Domingo

Por favor, lea atentamente esta hoja de información:

El PROMOTOR del estudio pretende desarrollar un proyecto de investigación que tiene como objetivo principal profundizar en el conocimiento de la importancia de la concentración de la IgE libre en sangre, después de la administración de Omalizumab, de cara al pronóstico de su enfermedad.
Este estudio requiere la utilización de muestras biológicas (sangre) obtenidas de sujetos que reúnen una serie de condiciones previas definidas en el protocolo por el promotor. Para ello, se va a utilizar sangre procedente de las analíticas de rutina que su médico decida realizarle.
Considerando la patología que padece y las condiciones que reúne, Vd. es un sujeto idóneo para participar en este proyecto de investigación.
Por ello, solicitamos su consentimiento para utilizar parte de la sangre extraida para realizar las determinaciones adicionales que el protocol especifica.

RIESGOS Y MOLESTIAS

Las molestias y riesgos de participar en este estudio están relacionados con la obtención de las muestra de sangre que su médico decida realizar en cada momento.
Por tanto las analíticas que se le realizarán forman parte de la práctica clínica habitual de su condición.

BENEFICIO Y ATENCIÓN MÉDICA

La cesión de muestras para investigación es voluntaria y altruista. Su único beneficio es el que corresponde al avance de la medicina en beneficio de la sociedad, y el saber que ha colaborado en este proceso. La muestra así recogida no podrá ser objeto directo de actividades con ánimo de lucro. Su participación en este estudio es completamente voluntaria. Si usted decide no participar recibirá todos los cuidados médicos que pudiera necesitar y su relación con los equipos médicos que le atiendan no se verá afectada.

DESTINO DE LA MUESTRA Y CESIÓN A OTRAS LINEAS DE INVESTIGACIÓN

Las muestras obtenidas no serán cedidas a terceros ni serán utilizadas con fines distintos a este proyecto de investigación.
El análisis de su sangre se realizará en el laboratorio habitual de la Corporació Parc Taulí, en la UDIAT (sección de inmunología) y en la Universidad de Munich (Dr. Markus Ollert).
Las muestras sobrantes serán destruidas una vez hayan sido analizadas.

Su médico, junto con la muestra, recogerá aquellos datos personales, como edad, sexo, raza, así como los datos de salud directamente relacionados con la patología por la que cual se le recoge la muestra para investigación. Sólo el MEDICO RESPONSABLE DE SUS CUIDADOS MÉDICOS podrá relacionar estos datos con Vd.
El hospital registrará los datos de su sangre de la manera habitual. Asimismo, sólo su médico será el responsable de custodiar el documento de consentimiento, y sólo a él le corresponde garantizar el cumplimiento de su voluntad en relación al uso de la muestra biológica que vd. cede a para investigación.
Su médico garantiza que en ningún caso saldrá del centro dato alguno que le identifique personalmente.

REVOCACIÓN DEL CONSENTIMIENTO

En cualquier momento podrá Vd. revocar el consentimiento para utilizar las muestras obtenidas, pudiendo solicitar la destrucción o la anonimización de las mismas. No obstante, los efectos de la revocación no se extenderán a los datos resultantes de las investigaciones que se hayan llevado a cabo previamente a la misma.
Puede ejercitar su derecho de acceso, rectificación y cancelación de dicha información dirigiéndose al Dr. C. Domingo
responsable de la realización del estudio en el centro.

DERECHOS Y GARANTÍAS

Usted tiene derecho a conocer los datos que se obtengan a partir del análisis de las muestras de sangre donadas.
Como consecuencia de la investigación puede obtenerse información relativa a su salud derivada de los análisis que se realicen sobre su sangre. Vd. puede decidir si desea recibir esta información, o si por el contrario renuncia a este derecho.
Asimismo, se le indica que la información que se obtenga puede implicar a sus familiares, siendo únicamente Vd. el responsable de facilitar, en su caso, información a los mismos, o proporcionar a las personas responsables del estudio los datos precisos para su localización y contacto.

CONFIDENCIALIDAD

Con la firma de este consentimiento, Vd. autoriza al investigador y al promotor, junto con el empleo de la muestra *biológica*, a recoger y procesar los datos personales agregados a la muestra, como son: fecha de nacimiento, sexo, origen étnico, y datos sobre su condición, relevantes para los fines de esta investigación.
Estos datos se someterán a un proceso de disociación mediante la asignación de un código, para garantizar la protección de su identidad.
Su médico y el promotor, en su caso, utilizarán estos datos para la realización de esta investigación.
Igualmente, el médico y el promotor podrán utilizar sus datos para apoyar ante las autoridades competentes o en las presentaciones públicas que realicen, los resultados de la investigación.
Los resultados del estudio podrán ser comunicados en reuniones científicas, congresos médicos o publicaciones científicas. Siempre se mantendrá una estricta confidencialidad sobre su identidad.
Tanto el médico como el Promotor son responsables del manejo de los Datos del Estudio, conforme el Real Decreto 223/2004 y la Ley Orgánica 15/1999, de 13 de diciembre, sobre Protección de Datos de Carácter Personal y el Real Decreto 1720/2007, de 21 de diciembre, por el que se aprueba el Reglamento de desarrollo de la Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal.

Asimismo, se dará cumplimiento a los requerimientos de la Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica, y la Ley 14/2007, de 3 de julio, de Investigación biomédica.
Los derechos de acceso, rectificación, cancelación y oposición puede ejercitarlos ante:
el Dr. C.Domingo.

Si tiene alguna duda relativa al estudio, por favor consulte a su médico.

Nombre del médico: Dr. C. Domingo.....

Teléfono de contacto: 93 723 10 10 .....

Se entregará una copia de la hoja de información al paciente y consentimiento informado al paciente.

10.5. Appendix 5: Patients' Informed Consent for sample release

CONSENTIMIENTO INFORMADO PARA LA CESIÓN DE MUESTRAS

Título del estudio: IgE libres como factor predictor de respuesta a omalizumab
Promotor del estudio: Dr. Christian Domingo
Código del estudio: FIS código CDR-OMA-2012-01/PI11/02303
Investigador Principal: Dr. Christian Domingo

Yo (paciente) …….....….....…
con DNI…..…….....… declaro bajo mi responsabilidad que he leído la hoja de Información al paciente y acepto participar en este estudio.

• Se me ha entregado una copia del documento "Hoja de Información al paciente para la cesión de muestras". En ella se me han explicado las características y el objetivo del estudio, así como los posibles beneficios y riesgos que puedo esperar.

• Se me ha dado tiempo y oportunidad para realizar preguntas. Todas las preguntas respondidas a mi entera satisfacción.

• Sé que se mantendrá en secreto mi identidad y que se identificarán mis muestras con un sistema de codificación.

• Soy libre de retirarme del estudio en cualquier momento por cualquier motivo, sin tener que dar explicación y sin que repercuta negativamente sobre cualquier tratamiento médico presente o futuro.

• Tras ello se procederá a la destrucción de la muestra codificada.

• Entiendo la finalidad del estudio y que los resultados del mismo no se comunicarán, excepto en el caso de que dichos hallazgos tengan una implicación significativa para la salud de los participantes y que exista una posibilidad real de mejorar esa condición de salud.

Yo **DOY mi consentimiento** para que se utilicen mis muestras y los datos asociados como parte de este proyecto de investigación. Consiento en participar voluntariamente y renuncio a reclamar cualquier beneficio económico por mi participación en el estudio.
Por la presente afirmo haber sido advertido sobre la posibilidad de recibir información relativa a mi salud derivada de los análisis que se realicen sobre mi muestra biológica.

☐ **Yo solicito información**

☐ **Yo no quiero recibir información**

una vez finalizada la investigación sobre los resultados del estudio.

Firma del/la participante: .....

Fecha: _____/_____/_____
Día *Mes* *Año*

Constato que he explicado las características del proyecto de investigación y las condiciones de conservación y seguridad que se aplicarán a la muestra y a los datos conservados.
Constato que he explicado las características de la cesión de muestras y la posible utilización de las mismas, así como las condiciones de conservación y seguridad que se aplicarán a la muestra y a los datos conservados.

Firma del investigador: .....

Fecha: _____/_____/_____
Día *Mes* *Año*

Por favor, recuerde que el formulario ha de ser completado POR EL/LA PARTICIPANTE, de su puño y letra.
El paciente debe recibir una copia de la hoja de información al paciente y consentimiento informado.
Muchas gracias por su colaboración

10.6. Appendix 6: Internal Review Board Acceptance

INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Doña COLOMA MORENO QUIROGA, Secretaria del Comité Ético de Investigación Clínica de la CORPORACIÓ SANITÀRIA PARC TAULÍ DE SABADELL (Barcelona)

CERTIFICA

Que este Comité ha evaluado la propuesta del promotor FIS código CDR-OMA-2012-01/PI11/02303 para que se realice el estudio titulado: "Protocolo de descenso progresivo de la dosis de omalizumab en
pacientes con asma alérgico corticodependiente; IgE libres como factor predictor." , protocolo v. 2, junio de 2012, CI v. 2, junio de 2012. En la sesión del10/07/2012, y considera que:

1. Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsible para el sujeto.
2. La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.
3. Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudiera derivarse de su participación en el estudio.
4. El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
5. Y que el Comité acepta que dicho estudio sea realizado en el Corporació Sanitària Parc Taulí de SABADELL por DOMINGO RIBAS CHRISTIAN, como investigador principal.

Lo que firma en SABADELL a martes, 10 julio 2012

Firmado:

Dra. Coloma Moreno Quiroga

Ref.: 2012573

10.7. Appendix 7: Tables-Support material

Table 1s: Longitudinal measures

Variable	Visit					
	0	1	2	3	4	5
Total IgE [IU/mL], Mean (SD)	285 (280)	777 (854)	630 (618)	565 (488)	546 (458)	514 (446)
FVC [%], Mean (SD)	77.4 (20.1)	80.7 (17.2)	73.8 (16.4)	76.4 (16.7)	76.9 (19.0)	75.9 (16.5)
FEV_1 [%], Mean (SD)	63.5 (20.5)	66.0 (18.3)	61.6 (18.6)	64.4 (20.0)	65.0 (20.3)	66.0 (21.1)
FEV_1/FVC ratio [%], Mean (SD)	62.9 (14.2)	63.6 (15.2)	62.7 (14.2)	63.1 (13.9)	64.1 (14.6)	64.7 (13.8)
Dose of omalizumab [mg], Mean (SD)	0.00 (0.00)	298 (114)	288 (120)	256 (116)	269 (134)	244 (160)
Dose of corticosteroids [mg], Mean (SD)	5.74 (5.13)	. (.)	. (.)	. (.)	. (.)	2.32 (4.00)
Free IgE [IU/mL], Mean (SD)	. (.)	6.62 (14.4)	. (.)	. (.)	. (.)	. (.)
Ratio Free:Total IgE [%], Mean (SD)	2.33 (3.74)	0.88 (1.71)	1.10 (2.34)	1.09 (1.73)	1.12 (1.74)	1.09 (1.51)
FEV_1 criterion, n (%):						
FEV_1 follow-up ≤ basal	0 (.%)	10 (32.3%)	19 (61.3%)	16 (51.6%)	13 (41.9%)	14 (45.2%)
FEV_1 follow-up > basal	0 (.%)	21 (67.7%)	12 (38.7%)	15 (48.4%)	18 (58.1%)	17 (54.8%)
Dose of corticosteroids criterion, n (%):						
Dose of corticosteroids follow-up ≥ basal	0 (.%)	0 (.%)	0 (.%)	0 (.%)	0 (.%)	15 (48.4%)
Dose of corticosteroids follow-up < basal	0 (.%)	0 (.%)	0 (.%)	0 (.%)	0 (.%)	16 (51.6%)
Dose of omalizumab criterion, n (%):						
Dose of omalizumab follow-up ≥ basal	0 (.%)	31 (100%)	29 (93.5%)	23 (74.2%)	23 (74.2%)	20 (64.5%)
Dose of omalizumab follow-up < basal	0 (.%)	0 (0.00%)	2 (6.45%)	8 (25.8%)	8 (25.8%)	11 (35.5%)
Omalizumab response, n (%):						
Non-responder	0 (.%)	0 (.%)	0 (.%)	0 (.%)	0 (.%)	7 (22.6%)
Responder	0 (.%)	0 (.%)	0 (.%)	0 (.%)	0 (.%)	24 (77.4%)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IU, international unit.

Table 2s: Measures by treatment response at visit 5 (Three criteria)

Variable	Non-responder	Responder	p-value
	N=7	*N=24*	
Sex, n (%):			0.658
Women	4 (57.1%)	17 (70.8%)	
Men	3 (42.9%)	7 (29.2%)	
Age at visit 0 [years], Mean (SD)	54.9 (18.5)	50.8 (16.8)	0.614
Weight [kg], Mean (SD)	72.4 (10.1)	73.1 (19.8)	0.901
Height [cm], Mean (SD)	161 (9.83)	160 (9.92)	0.707
BMI [kg/m2], Mean (SD)	27.9 (4.05)	28.5 (6.52)	0.782
Total IgE visit 0 [IU/mL], Mean (SD)	228 (144)	302 (309)	0.383
FVC visit 0 [%], Mean (SD)	86.6 (19.5)	74.7 (19.9)	0.188
FEV_1 visit 0 [%], Mean (SD)	74.1 (17.0)	60.4 (20.6)	0.099
FEV_1/FVC ratio visit 0 [%], Mean (SD)	66.4 (17.2)	61.8 (13.5)	0.533
Dose of corticosteroids visit 0 [mg], Mean (SD)	3.14 (6.09)	6.50 (4.69)	0.214
Total IgE visit 1 [IU/mL], Mean (SD)	539 (339)	847 (948)	0.196
FVC visit 1 [%], Mean (SD)	82.7 (9.74)	80.1 (19.0)	0.633
FEV_1 visit 1 [%], Mean (SD)	70.3 (12.5)	64.8 (19.7)	0.389
FEV_1/FVC ratio visit 1 [%], Mean (SD)	64.9 (15.6)	63.2 (15.4)	0.810
Dose of omalizumab visit 1 [mg], Mean (SD)	289 (80.2)	300 (123)	0.789
Total IgE visit 2 [IU/mL], Mean (SD)	547 (342)	655 (681)	0.577
FVC visit 2 [%], Mean (SD)	73.0 (10.9)	74.0 (17.9)	0.858
FEV_1 visit 2 [%], Mean (SD)	58.0 (15.7)	62.6 (19.6)	0.529
FEV_1/FVC ratio visit 2 [%], Mean (SD)	59.7 (17.2)	63.6 (13.5)	0.598
Dose of omalizumab visit 2 [mg], Mean (SD)	289 (80.2)	288 (130)	0.965
Total IgE visit 3 [IU/mL], Mean (SD)	499 (324)	585 (531)	0.606
FVC visit 3 [%], Mean (SD)	71.4 (7.39)	77.8 (18.5)	0.184
FEV_1 visit 3 [%], Mean (SD)	57.3 (14.9)	66.5 (21.1)	0.215
FEV_1/FVC ratio visit 3 [%], Mean (SD)	60.0 (17.0)	64.0 (13.2)	0.580
Dose of omalizumab visit 3 [mg], Mean (SD)	268 (121)	253 (117)	0.782
Total IgE visit 4 [IU/mL], Mean (SD)	679 (596)	507 (417)	0.497
FVC visit 4 [%], Mean (SD)	67.7 (19.1)	79.5 (18.5)	0.179
FEV_1 visit 4 [%], Mean (SD)	53.6 (16.2)	68.4 (20.4)	0.068
FEV_1/FVC ratio visit 4 [%], Mean (SD)	60.6 (16.6)	65.1 (14.1)	0.526
Dose of omalizumab visit 4 [mg], Mean (SD)	364 (170)	241 (111)	0.109
Total IgE visit 5 [IU/mL], Mean (SD)	563 (417)	500 (462)	0.739
FVC visit 5 [%], Mean (SD)	70.9 (9.63)	77.3 (17.9)	0.224
FEV_1 visit 5 [%], Mean (SD)	58.3 (17.6)	68.3 (21.9)	0.236
FEV_1/FVC ratio visit 5 [%], Mean (SD)	61.6 (18.0)	65.6 (12.6)	0.592
Dose of omalizumab visit 5 [mg], Mean (SD)	364 (170)	209 (142)	0.057
Dose of corticosteroids visit 5 [mg], Mean (SD)	3.14 (6.09)	2.08 (3.31)	0.672
Free IgE visit 1 [IU/mL], Mean (SD)	3.21 (4.98)	7.62 (16.1)	0.254
Ratio Free:Total IgE visit 0 [%], Mean (SD)	1.60 (1.93)	2.55 (4.13)	0.403
Ratio Free:Total IgE visit 1 [%], Mean (SD)	0.73 (0.87)	0.93 (1.90)	0.700
Ratio Free:Total IgE visit 2 [%], Mean (SD)	0.78 (0.94)	1.20 (2.62)	0.514

Variable	Non-responder	Responder	p-value
	N=7	*N=24*	
Ratio Free:Total IgE visit 3 [%], Mean (SD)	1.02 (1.33)	1.11 (1.85)	0.898
Ratio Free:Total IgE visit 4 [%], Mean (SD)	0.74 (0.91)	1.23 (1.92)	0.354
Ratio Free:Total IgE visit 5 [%], Mean (SD)	0.78 (0.91)	1.18 (1.65)	0.412
FEV_1 criterion visit 1, n (%):			0.658
FEV_1 follow-up ≤ basal	3 (42.9%)	7 (29.2%)	
FEV_1 follow-up > basal	4 (57.1%)	17 (70.8%)	
FEV_1 criterion visit 2, n (%):			0.200
FEV_1 follow-up ≤ basal	6 (85.7%)	13 (54.2%)	
FEV_1 follow-up > basal	1 (14.3%)	11 (45.8%)	
FEV_1 criterion visit 3, n (%):			0.004
FEV_1 follow-up ≤ basal	7 (100%)	9 (37.5%)	
FEV_1 follow-up > basal	0 (0.00%)	15 (62.5%)	
FEV_1 criterion visit 4, n (%):			0.105
FEV_1 follow-up ≤ basal	5 (71.4%)	8 (33.3%)	
FEV_1 follow-up > basal	2 (28.6%)	16 (66.7%)	
FEV_1 criterion visit 5, n (%):			0.002
FEV_1 follow-up ≤ basal	7 (100%)	7 (29.2%)	
FEV_1 follow-up > basal	0 (0.00%)	17 (70.8%)	
Dose of corticosteroids criterion visit 5, n (%):			0.002
Dose of corticosteroids follow-up ≥ basal	7 (100%)	8 (33.3%)	
Dose of corticosteroids follow-up < basal	0 (0.00%)	16 (66.7%)	
Dose of omalizumab criterion visit 1, n (%):			.
Dose of omalizumab follow-up ≥ basal	7 (100%)	24 (100%)	
Dose of omalizumab follow-up < basal	0 (0.00%)	0 (0.00%)	
Dose of omalizumab criterion visit 2, n (%):			>0.999
Dose of omalizumab follow-up ≥ basal	7 (100%)	22 (91.7%)	
Dose of omalizumab follow-up < basal	0 (0.00%)	2 (8.33%)	
Dose of omalizumab criterion visit 3, n (%):			>0.999
Dose of omalizumab follow-up ≥ basal	5 (71.4%)	18 (75.0%)	
Dose of omalizumab follow-up < basal	2 (28.6%)	6 (25.0%)	
Dose of omalizumab criterion visit 4, n (%):			0.138
Dose of omalizumab follow-up ≥ basal	7 (100%)	16 (66.7%)	
Dose of omalizumab follow-up < basal	0 (0.00%)	8 (33.3%)	
Dose of omalizumab criterion visit 5, n (%):			0.072
Dose of omalizumab follow-up ≥ basal	7 (100%)	13 (54.2%)	
Dose of omalizumab follow-up < basal	0 (0.00%)	11 (45.8%)	

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IU, international unit.

Table 3s: Measures by treatment response at visit 5 (omalizumab criterion)

Variable	Dose of omalizumab follow-up ≥ basal	Dose of omalizumab follow-up < basal	p-value
	N=20	*N=11*	
Sex, n (%):			>0.999
Women	14 (70.0%)	7 (63.6%)	
Men	6 (30.0%)	4 (36.4%)	
Age at visit 0 [years], Mean (SD)	52.2 (15.4)	50.9 (20.3)	0.860
Weight [kg], Mean (SD)	74.4 (19.8)	70.3 (14.3)	0.504
Height [cm], Mean (SD)	161 (7.70)	159 (13.1)	0.730
BMI [kg/m2], Mean (SD)	28.6 (6.36)	27.8 (5.53)	0.719
Total IgE visit 0 [IU/mL], Mean (SD)	271 (256)	310 (330)	0.739
FVC visit 0 [%], Mean (SD)	79.5 (23.4)	73.5 (12.4)	0.355
FEV_1 visit 0 [%], Mean (SD)	64.8 (22.5)	61.0 (17.0)	0.596
FEV_1/FVC ratio visit 0 [%], Mean (SD)	61.9 (13.0)	64.6 (16.8)	0.645
Dose of corticosteroids visit 0 [mg], Mean (SD)	4.70 (4.55)	7.64 (5.78)	0.164
Total IgE visit 1 [IU/mL], Mean (SD)	695 (799)	926 (969)	0.510
FVC visit 1 [%], Mean (SD)	82.3 (18.8)	77.8 (14.2)	0.462
FEV_1 visit 1 [%], Mean (SD)	65.2 (18.7)	67.6 (18.2)	0.722
FEV_1/FVC ratio visit 1 [%], Mean (SD)	61.3 (13.3)	67.7 (18.1)	0.316
Dose of omalizumab visit 1 [mg], Mean (SD)	278 (73.4)	334 (162)	0.293
Total IgE visit 2 [IU/mL], Mean (SD)	630 (718)	631 (404)	0.996
FVC visit 2 [%], Mean (SD)	73.7 (15.1)	73.9 (19.4)	0.976
FEV_1 visit 2 [%], Mean (SD)	59.0 (16.7)	66.2 (21.7)	0.358
FEV_1/FVC ratio visit 2 [%], Mean (SD)	60.5 (13.7)	66.6 (14.8)	0.275
Dose of omalizumab visit 2 [mg], Mean (SD)	270 (78.5)	320 (171)	0.373
Total IgE visit 3 [IU/mL], Mean (SD)	598 (574)	507 (286)	0.562
FVC visit 3 [%], Mean (SD)	75.4 (14.4)	78.1 (21.0)	0.715
FEV_1 visit 3 [%], Mean (SD)	62.9 (18.3)	67.2 (23.6)	0.608
FEV_1/FVC ratio visit 3 [%], Mean (SD)	62.4 (13.8)	64.5 (14.7)	0.701
Dose of omalizumab visit 3 [mg], Mean (SD)	285 (116)	205 (101)	0.056
Total IgE visit 4 [IU/mL], Mean (SD)	600 (540)	447 (241)	0.285
FVC visit 4 [%], Mean (SD)	74.9 (18.5)	80.5 (20.1)	0.459
FEV_1 visit 4 [%], Mean (SD)	62.0 (18.5)	70.6 (22.9)	0.296
FEV_1/FVC ratio visit 4 [%], Mean (SD)	63.1 (14.5)	65.9 (15.3)	0.623

Variable	Dose of omalizumab follow-up ≥ basal	Dose of omalizumab follow-up < basal	p-value
	N=20	*N=11*	
Dose of omalizumab visit 4 [mg], Mean (SD)	319 (137)	177 (60.7)	<0.001
Total IgE visit 5 [IU/mL], Mean (SD)	589 (522)	378 (219)	0.127
FVC visit 5 [%], Mean (SD)	75.3 (15.5)	76.8 (19.0)	0.829
FEV_1 visit 5 [%], Mean (SD)	64.4 (20.6)	68.9 (22.8)	0.596
FEV_1/FVC ratio visit 5 [%], Mean (SD)	63.7 (14.3)	66.5 (13.1)	0.582
Dose of omalizumab visit 5 [mg], Mean (SD)	319 (137)	109 (97.0)	<0.001
Dose of corticosteroids visit 5 [mg], Mean (SD)	3.10 (4.70)	0.91 (1.64)	0.071
Free IgE visit 1 [IU/mL], Mean (SD)	8.06 (17.0)	4.01 (7.78)	0.373
Ratio Free:Total IgE visit 0 [%], Mean (SD)	2.63 (4.39)	1.79 (2.20)	0.486
Ratio Free:Total IgE visit 1 [%], Mean (SD)	1.17 (2.09)	0.37 (0.27)	0.109
Ratio Free:Total IgE visit 2 [%], Mean (SD)	1.42 (2.87)	0.53 (0.50)	0.187
Ratio Free:Total IgE visit 3 [%], Mean (SD)	1.30 (2.07)	0.70 (0.73)	0.257
Ratio Free:Total IgE visit 4 [%], Mean (SD)	1.27 (2.07)	0.83 (0.89)	0.418
Ratio Free:Total IgE visit 5 [%], Mean (SD)	1.17 (1.76)	0.94 (0.96)	0.632
FEV_1 criterion visit 1, n (%):			0.711
FEV_1 follow-up ≤ basal	7 (35.0%)	3 (27.3%)	
FEV_1 follow-up > basal	13 (65.0%)	8 (72.7%)	
FEV_1 criterion visit 2, n (%):			0.708
FEV_1 follow-up ≤ basal	13 (65.0%)	6 (54.5%)	
FEV_1 follow-up > basal	7 (35.0%)	5 (45.5%)	
FEV_1 criterion visit 3, n (%):			0.376
FEV_1 follow-up ≤ basal	12 (60.0%)	4 (36.4%)	
FEV_1 follow-up > basal	8 (40.0%)	7 (63.6%)	
FEV_1 criterion visit 4, n (%):			0.721
FEV_1 follow-up ≤ basal	9 (45.0%)	4 (36.4%)	
FEV_1 follow-up > basal	11 (55.0%)	7 (63.6%)	
FEV_1 criterion visit 5, n (%):			0.709
FEV_1 follow-up ≤ basal	10 (50.0%)	4 (36.4%)	
FEV_1 follow-up > basal	10 (50.0%)	7 (63.6%)	
Dose of corticosteroids criterion visit 5, n (%):			0.034
Dose of corticosteroids follow-up ≥ basal	13 (65.0%)	2 (18.2%)	

Variable	Dose of omalizumab follow-up ≥ basal	Dose of omalizumab follow-up < basal	p-value
	N=20	*N=11*	
Dose of corticosteroids follow-up < basal	7 (35.0%)	9 (81.8%)	
Dose of omalizumab criterion visit 1, n (%):			.
Dose of omalizumab follow-up ≥ basal	20 (100%)	11 (100%)	
Dose of omalizumab follow-up < basal	0 (0.00%)	0 (0.00%)	
Dose of omalizumab criterion visit 2, n (%):			>0.999
Dose of omalizumab follow-up ≥ basal	19 (95.0%)	10 (90.9%)	
Dose of omalizumab follow-up < basal	1 (5.00%)	1 (9.09%)	
Dose of omalizumab criterion visit 3, n (%):			0.009
Dose of omalizumab follow-up ≥ basal	18 (90.0%)	5 (45.5%)	
Dose of omalizumab follow-up < basal	2 (10.0%)	6 (54.5%)	
Dose of omalizumab criterion visit 4, n (%):			<0.001
Dose of omalizumab follow-up ≥ basal	20 (100%)	3 (27.3%)	
Dose of omalizumab follow-up < basal	0 (0.00%)	8 (72.7%)	
Omalizumab response at visit 5, n (%):			0.072
Non-responder	7 (35.0%)	0 (0.00%)	
Responder	13 (65.0%)	11 (100%)	

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IU, international unit.

10.8. Appendix 8: Evolution in the FVC, FEV1, IgE and omalizumab dose according to their response (three criteria)

A- FVC changes

VISIT:	0	1	2	3	4	5
Non Responder						
Mean	86.57143	82.714286	73.00000	71.42857	67.71429	70.85714
SD	19.49237	9.741908	10.92398	7.39047	19.11992	9.63377
P25	79.50000	78.500000	66.00000	67.00000	59.00000	65.00000
Median	86.00000	82.000000	66.00000	72.00000	64.00000	71.00000
P75	96.00000	88.000000	81.50000	75.00000	76.00000	75.50000
Min	53.00000	68.000000	61.00000	61.00000	40.00000	58.00000
Max	116.00000	96.000000	89.00000	83.00000	100.00000	86.00000
Responder						
Mean	74.66667	80.125000	74.00000	77.83333	79.54167	77.33333
SD	19.91431	18.960629	17.89340	18.46187	18.46496	17.90474
P25	68.75000	68.750000	61.00000	61.75000	66.75000	60.50000
Median	72.50000	86.000000	77.00000	80.00000	78.50000	78.00000
P75	89.50000	95.250000	87.25000	94.50000	93.25000	91.75000
Min	26.00000	34.000000	44.00000	45.00000	45.00000	45.00000
Max	110.00000	105.000000	109.00000	110.00000	116.00000	104.00000

B- FEV1 changes

VISIT:	0	1	2	3	4	5
Non Responder						
Mean	74.14286	70.28571	58.00000	57.28571	53.57143	58.28571
SD	17.00420	12.48618	15.65248	14.89647	16.17464	17.60411
P25	62.50000	60.50000	46.50000	47.00000	41.50000	45.00000
Median	80.00000	66.00000	59.00000	61.00000	56.00000	57.00000
P75	85.50000	79.50000	70.00000	65.00000	65.00000	67.00000
Min	48.00000	57.00000	36.00000	36.00000	31.00000	39.00000
Max	95.00000	89.00000	78.00000	80.00000	75.00000	88.00000
Responedor						
Mean	60.37500	64.79167	62.62500	66.50000	68.37500	68.29167
SD	20.64148	19.69105	19.57774	21.10430	20.40207	21.85820
P25	45.00000	53.50000	50.50000	53.25000	54.00000	54.50000
Median	61.00000	65.00000	61.00000	69.00000	77.00000	68.50000
P75	76.75000	76.25000	81.50000	84.25000	84.00000	82.00000
Min	18.00000	20.00000	20.00000	20.00000	20.00000	20.00000
Max	94.00000	106.00000	91.00000	103.00000	97.00000	106.00000

C-Total IgE changes

Vist:	0	1	2	3	4	5
Non responder						
Mean	227.5714	538.8571	547.1429	499.0000	678.5714	562.5714
SD	144.4713	339.0489	342.4234	323.7324	595.8000	416.8332
P25	132.0000	309.0000	299.5000	253.0000	283.0000	305.0000
Median	152.0000	479.0000	531.0000	385.0000	391.0000	401.0000
P75	298.0000	671.5000	691.0000	754.5000	981.0000	747.0000
Mín	92.0000	167.0000	188.0000	139.0000	187.0000	125.0000
Max	489.0000	1165.0000	1130.0000	954.0000	1644.0000	1308.0000
Responder						
Mean	301.7000	846.7625	654.7458	584.8708	507.1542	499.8583
SD	308.6078	948.2682	681.2330	530.7742	416.7790	461.8883
P25	104.7500	339.0000	307.0000	239.0000	227.7500	198.5000
Median	184.0000	562.5000	449.5000	430.0000	425.5000	405.0000
P75	364.0000	849.2500	652.0000	728.7500	701.7500	620.5000
Min	36.7000	26.3000	68.9000	66.9000	65.1000	61.2000
Max	1175.0000	3746.0000	3289.0000	2481.0000	1814.0000	1948.0000

D- Omalizumab dose changes

VISIT:	0	1	2	3	4	5
Non Responder						
Mean	0	289.28571	289.28571	267.8571	364.2857	364.2857
SD	0	80.17837	80.17837	121.3760	170.0840	170.0840
P25	0	262.50000	262.50000	150.0000	300.0000	300.0000
Median	0	300.00000	300.00000	300.0000	300.0000	300.0000
P75	0	337.50000	337.50000	337.5000	450.0000	450.0000
Min	0	150.00000	150.00000	150.0000	150.0000	150.0000
Max	**0**	**375.00000**	**375.00000**	**450.0000**	**600.0000**	**600.0000**
Responder						
Mean	0	300.00000	287.50000	253.1250	240.6250	209.3750
SD	0	123.13831	130.21721	116.6359	110.5354	141.5774
P25	0	300.00000	150.00000	150.0000	150.0000	150.0000
Median	0	300.00000	300.00000	300.0000	225.0000	150.0000
P75	0	300.00000	300.00000	300.0000	300.0000	300.0000
Min	0	150.00000	150.00000	0.0000	150.0000	0.0000
Max	**0**	**750.00000**	**750.00000**	**600.0000**	**600.0000**	**600.0000**

10.9. Appendix 9: Database

NHC	naixement	age	height	weight	sex	data_prova	FEV1	FVC	FEV1/FVC	%_FEV1	%_FVC
*****	*******	46	171	87	F	27/05/2019	1,76	3,04	57,00	55,52	77,04
*****	*******	46	171	87	F	31/07/2019	2,30	3,41	67,00	72,40	86,43
*****	*******	46	171	86	F	29/08/2019	2,18	3,28	66,00	68,87	83,11
*****	*******	46	171	88	F	26/09/2019	2,03	3,20	63,00	63,90	80,92
*****	*******	49	172	70	F	23/06/2022	2,21	3,50	63,10	70,17	88,53
*****	*******	49	172	70	F	25/08/2022	2,29	3,62	63,31	72,75	91,48
*****	*******	50	172	70	F	17/11/2022	2,20	3,47	63,45	70,70	88,54
*****	*******	50	172	70	F	09/02/2023	2,43	3,41	71,39	78,00	86,81
*****	*******	50	172	70	F	04/05/2023	2,05	3,22	63,51	65,62	82,10
*****	*******	50	172	70	F	20/07/2023	2,26	3,62	62,40	72,35	92,13
*****	*******	50	172	70	F	05/10/2023	2,28	3,59	63,53	73,19	91,55
*****	*******	19	171	68	M	11/10/2018	3,58	4,32	82,00	83,85	82,83
*****	*******	26	164	89	F	29/03/2017	2,03	3,17	64,09	61,07	81,60
*****	*******	26	164	89	F	11/04/2017	3,49	4,10	84,96	104,70	105,52
*****	*******	26	164	89	F	26/04/2017	1,91	3,09	61,98	57,51	79,44
*****	*******	26	164	89	F	02/05/2017	3,97	4,69	84,69	119,31	120,63
*****	*******	26	164	89	F	10/05/2017	2,82	3,31	85,17	84,75	85,20
*****	*******	29	164	89	F	01/10/2020	2,36	3,01	78,59	71,86	77,49
*****	*******	30	164	89	F	29/10/2020	2,29	3,21	71,38	70,09	82,95
*****	*******	30	164	89	F	26/11/2020	1,92	2,59	73,96	58,63	66,96
*****	*******	30	164	89	F	18/02/2021	2,47	3,49	70,96	75,60	90,00
*****	*******	30	164	89	F	13/05/2021	1,55	2,09	73,91	47,23	53,97
*****	*******	31	164	89	F	27/01/2022	1,80	2,48	72,53	55,16	64,02
*****	*******	31	164	89	F	28/04/2022	2,31	3,04	75,85	70,77	78,55
*****	*******	32	164	89	F	27/10/2022	1,69	2,22	75,88	52,07	57,59
*****	*******	32	164	89	F	10/11/2022	1,56	1,59	97,76	48,01	41,22
*****	*******	32	164	89	F	24/11/2022	1,63	2,07	78,59	50,16	53,57
*****	*******	32	164	89	F	22/12/2022	1,90	2,65	71,60	58,54	68,61
*****	*******	32	164	89	F	19/01/2023	1,47	2,20	67,01	45,41	56,88
*****	*******	32	164	89	F	16/02/2023	1,93	2,32	83,35	59,54	59,95
*****	*******	32	164	89	F	22/06/2023	1,35	1,83	73,78	41,75	47,49
*****	*******	20	179	64	M	18/10/2018	4,24	4,81	88,00	90,80	83,06
*****	*******	20	179	64	M	11/04/2019	4,15	4,84	85,00	89,13	83,75
*****	*******	21	179	66	M	17/10/2019	3,82	4,70	81,00	82,10	81,39
*****	*******	22	180	75	M	17/09/2020	4,43	5,15	85,99	92,19	90,19
*****	*******	22	180	75	M	14/01/2021	4,29	4,99	85,92	89,35	87,49
*****	*******	22	180	75	M	06/05/2021	4,27	4,96	85,98	88,85	86,93
*****	*******	23	180	75	M	28/10/2021	4,21	4,94	85,15	87,76	86,45
*****	*******	23	180	75	M	16/06/2022	3,88	4,66	83,18	80,92	81,61
*****	*******	24	180	75	M	06/10/2022	4,05	4,93	82,04	84,71	86,37
*****	*******	24	180	75	M	26/01/2023	4,24	4,98	85,15	88,82	87,25
*****	*******	24	180	75	M	18/05/2023	4,35	5,03	86,49	90,98	88,00
*****	*******	44	185	86	M	16/11/2015	4,32	5,98	72,00	96,56	102,33
*****	*******	44	185	85	M	15/02/2016	3,79	5,18	73,00	84,87	88,65
*****	*******	45	185	86	M	17/05/2016	4,73	6,69	70,00	106,26	114,75
*****	*******	45	185	84	M	08/08/2016	4,52	6,02	75,00	101,53	103,31
*****	*******	45	185	85	M	15/11/2016	4,19	5,87	71,00	94,26	100,73
*****	*******	45	185	86	M	15/02/2017	3,51	5,03	69,00	78,86	86,26
*****	*******	46	185	88	M	23/05/2017	3,87	5,28	73,00	87,52	90,95
*****	*******	46	185	87	M	22/08/2017	4,50	5,95	75,00	101,83	102,48
*****	*******	46	185	87	M	16/11/2017	4,51	5,94	75,00	102,37	102,49
*****	*******	46	186	90	M	08/02/2018	3,84	5,43	70,64	85,74	95,47
*****	*******	47	185	87	M	24/05/2018	4,38	5,81	75,00	99,65	100,34
*****	*******	47	185	87	M	18/10/2018	4,47	6,03	74,00	101,80	104,06
*****	*******	47	185	87	M	21/03/2019	4,22	6,21	67,00	96,34	107,51
*****	*******	48	185	87	M	13/06/2019	4,11	5,56	73,00	93,87	96,16
*****	*******	49	186	90	M	15/10/2020	2,94	4,75	61,82	67,05	84,88
*****	*******	49	186	90	M	14/01/2021	4,36	5,79	75,31	99,49	103,40
*****	*******	50	186	90	M	08/04/2021	4,47	6,05	73,81	102,82	108,83
*****	*******	50	186	90	M	16/09/2021	4,19	5,60	74,71	96,32	100,72
*****	*******	50	186	90	M	16/12/2021	4,31	5,79	74,50	99,25	104,07
*****	*******	50	186	90	M	10/03/2022	4,05	5,93	68,31	93,29	106,69
*****	*******	51	186	90	M	09/06/2022	4,45	5,99	74,21	103,11	108,36
*****	*******	51	186	90	M	15/09/2022	4,05	5,56	72,81	93,86	100,54
*****	*******	51	186	90	M	15/12/2022	3,74	5,23	71,37	86,67	94,70
*****	*******	51	186	90	M	16/03/2023	3,83	5,51	69,52	88,78	99,60
*****	*******	52	186	90	M	08/06/2023	3,88	5,57	69,70	90,83	101,44
*****	*******	52	186	90	M	31/08/2023	3,65	5,27	69,17	85,28	95,98
*****	*******	52	186	90	M	26/10/2023	3,78	5,17	73,12	88,38	94,09

*****	*******	52	186	90 M	23/11/2023	3,66	5,10	71,90	85,69	92,78
*****	*******	52	186	90 M	21/12/2023	4,02	5,82	69,04	94,00	105,98
*****	*******	52	186	90 M	18/01/2024	4,15	5,54	74,90	97,13	100,94
*****	*******	52	186	90 M	15/02/2024	4,43	6,02	73,52	103,56	109,66
*****	*******	41	179	93 M	10/08/2016	2,78	4,48	62,00	65,64	81,75
*****	*******	41	179	94 M	24/08/2016	3,42	4,85	70,00	80,82	88,41
*****	*******	41	179	94 M	09/09/2016	2,94	4,59	64,00	69,50	83,68
*****	*******	41	179	99 M	05/10/2016	3,15	4,78	65,00	74,57	87,31
*****	*******	41	179	100 M	02/11/2016	3,16	4,73	66,00	74,74	86,27
*****	*******	41	179	102 M	30/11/2016	3,27	4,88	67,00	77,38	88,99
*****	*******	42	179	95 M	06/04/2017	3,14	4,62	67,00	74,59	84,61
*****	*******	42	179	90 M	28/06/2017	3,27	5,30	61,00	77,69	97,02
*****	*******	42	179	85 M	18/10/2017	2,55	4,44	57,00	60,86	81,42
*****	*******	42	179	89 M	17/01/2018	2,67	4,39	60,00	63,63	80,48
*****	*******	43	179	89 M	12/04/2018	2,20	4,02	54,00	52,68	73,77
*****	*******	43	179	87 M	18/07/2018	2,78	4,49	61,00	66,60	82,47
*****	*******	43	179	90 M	10/10/2018	2,75	4,82	57,00	65,83	88,55
*****	*******	43	179	89 M	09/01/2019	2,83	4,52	62,00	67,87	83,07
*****	*******	44	179	90 M	07/08/2019	2,65	4,44	59,00	63,60	81,81
*****	*******	45	180	99 M	14/01/2021	1,96	3,26	60,23	46,84	61,68
*****	*******	46	180	99 M	22/04/2021	2,00	3,58	55,83	48,06	68,15
*****	*******	46	180	99 M	20/05/2021	2,28	3,95	57,81	54,82	75,08
*****	*******	46	180	99 M	15/07/2021	2,16	3,97	54,42	51,95	75,57
*****	*******	46	180	99 M	07/10/2021	2,04	3,81	53,57	49,02	72,45
*****	*******	46	180	99 M	30/12/2021	2,20	4,01	54,96	52,94	76,27
*****	*******	47	180	99 M	24/03/2022	3,06	4,79	63,73	73,94	91,69
*****	*******	47	180	99 M	22/09/2022	2,34	3,87	60,40	56,59	74,03
*****	*******	47	180	99 M	22/12/2022	2,27	3,60	63,19	55,06	68,85
*****	*******	48	180	99 M	16/03/2023	3,00	4,70	63,84	73,09	90,32
*****	*******	48	180	99 M	15/06/2023	2,74	4,33	63,21	66,79	83,35
*****	*******	48	180	99 M	07/09/2023	2,58	4,12	62,55	62,78	79,18
*****	*******	40	160	108 F	21/10/2015	2,57	3,20	80,00	90,36	88,80
*****	*******	40	160	113 F	25/01/2016	2,43	2,99	81,00	85,59	83,10
*****	*******	40	160	110 F	20/04/2016	2,01	2,44	82,00	70,84	67,65
*****	*******	41	160	111 F	11/07/2016	2,43	2,97	81,00	86,24	83,31
*****	*******	41	160	116 F	06/10/2016	2,33	2,80	83,00	82,77	78,54
*****	*******	41	160	116 F	02/02/2017	2,28	2,69	84,00	80,85	75,41
*****	*******	41	160	120 F	26/05/2017	2,18	2,56	85,00	77,34	71,81
*****	*******	42	160	125 F	25/08/2017	2,01	2,43	82,00	69,99	68,37
*****	*******	42	160	125 F	16/11/2017	2,27	2,69	84,00	79,46	76,06
*****	*******	42	160	127 F	08/02/2018	2,27	2,73	83,00	79,53	77,12
*****	*******	42	160	120 F	03/05/2018	1,90	2,46	77,00	66,53	69,63
*****	*******	43	160	116 F	06/09/2018	2,17	2,63	82,00	76,45	74,62
*****	*******	43	160	99 F	13/12/2018	2,10	2,62	80,00	74,18	74,43
*****	*******	43	160	88 F	07/03/2019	2,41	3,00	80,00	85,01	85,22
*****	*******	43	160	80 F	27/06/2019	2,40	2,91	82,00	84,93	82,94
*****	*******	45	156	81 F	17/09/2020	2,50	3,12	80,08	94,25	95,77
*****	*******	45	156	81 F	10/12/2020	1,76	2,47	71,52	66,56	75,72
*****	*******	45	156	81 F	04/03/2021	2,23	3,06	72,87	84,22	94,04
*****	*******	46	156	81 F	14/10/2021	2,22	2,87	77,33	84,35	88,52
*****	*******	46	156	81 F	30/12/2021	2,35	2,98	78,90	89,36	91,92
*****	*******	46	156	81 F	21/04/2022	2,36	3,06	77,15	89,83	94,49
*****	*******	47	156	81 F	14/07/2022	1,91	2,82	67,61	73,26	87,76
*****	*******	47	156	81 F	13/10/2022	2,29	2,95	77,42	87,75	91,81
*****	*******	47	156	81 F	05/01/2023	2,31	3,01	76,96	88,81	93,48
*****	*******	47	156	81 F	30/03/2023	2,03	2,72	74,75	78,04	84,56
*****	*******	47	156	81 F	22/06/2023	2,31	2,90	79,73	88,87	90,29
*****	*******	48	156	81 F	14/09/2023	2,31	2,93	78,89	89,67	91,87
*****	*******	48	156	81 F	14/12/2023	2,25	2,70	83,21	87,13	84,64
*****	*******	41	165	86 M	08/02/2019	1,40	2,31	60,00	39,87	51,21
*****	*******	42	165	86 M	31/05/2019	1,32	2,18	60,00	37,57	48,25
*****	*******	42	165	85 M	09/07/2019	1,94	2,79	69,00	55,33	61,95
*****	*******	42	165	85 M	30/07/2019	2,40	3,28	73,00	68,50	72,83
*****	*******	42	165	80 M	27/09/2019	2,13	2,98	71,00	60,85	65,97
*****	*******	42	165	76 M	28/10/2019	2,51	3,51	71,00	71,79	77,90
*****	*******	43	166	86 M	11/02/2021	2,64	3,70	71,26	74,32	84,38
*****	*******	44	166	86 M	02/09/2021	2,27	3,27	69,49	64,44	74,88
*****	*******	44	166	86 M	25/11/2021	2,41	3,39	71,08	68,38	77,68
*****	*******	44	166	86 M	24/03/2022	2,44	3,43	71,27	69,31	78,53
*****	*******	45	166	86 M	16/06/2022	2,34	3,38	69,27	66,95	77,88

*****	*******	45	166	86	M	01/09/2022	2,19	3,25	67,27	62,50	74,87
*****	*******	46	166	86	M	04/08/2023	2,27	3,43	66,41	65,42	79,21
*****	*******	42	169	88	F	07/03/2018	1,78	2,78	64,00	55,20	70,14
*****	*******	42	170	89	F	21/03/2018	1,76	2,72	64,00	53,96	67,98
*****	*******	42	170	89	F	04/04/2018	1,82	2,64	68,00	55,97	65,96
*****	*******	42	170	91	F	19/04/2018	1,99	2,84	70,00	61,14	70,92
*****	*******	42	170	92	F	16/05/2018	1,89	2,87	65,00	58,07	71,63
*****	*******	42	170	92	F	15/06/2018	2,52	3,40	74,00	77,56	84,89
*****	*******	42	170	95	F	24/07/2018	2,05	2,88	71,00	63,11	72,00
*****	*******	42	170	94	F	23/08/2018	2,10	2,89	72,00	64,63	72,26
*****	*******	42	170	90	F	13/12/2018	1,85	2,12	87,00	57,16	53,26
*****	*******	56	164	88	F	21/09/2015	2,24	2,96	75,00	87,23	86,16
*****	*******	56	164	89	F	17/12/2015					
*****	*******	56	164	89	F	17/12/2015	2,29	3,29	69,00	88,98	95,67
*****	*******	56	164	83	F	18/03/2016	1,70	2,56	66,00	66,18	74,44
*****	*******	56	164	80	F	16/06/2016	1,93	2,69	71,00	74,98	78,18
*****	*******	57	164	80	F	12/09/2016	2,16	2,84	76,00	85,08	83,14
*****	*******	57	164	80	F	12/12/2016	2,11	3,08	68,00	83,01	90,08
*****	*******	57	164	80	F	13/03/2017	2,16	3,07	70,00	85,16	89,84
*****	*******	57	164	80	F	06/06/2017	2,16	3,12	69,00	84,85	91,34
*****	*******	58	164	80	F	24/08/2017	1,84	2,69	68,00	70,79	79,37
*****	*******	58	164	80	F	23/11/2017	1,87	2,71	69,00	72,28	79,88
*****	*******	58	164	83	F	15/02/2018	1,62	2,75	58,00	62,63	81,34
*****	*******	58	164	86	F	10/05/2018	1,98	2,79	70,00	76,93	82,56
*****	*******	59	164	87	F	27/09/2018	1,69	2,54	66,00	65,59	75,49
*****	*******	59	164	84	F	21/02/2019	1,63	2,46	66,00	63,97	73,18
*****	*******	59	164	84	F	23/05/2019	1,29	2,17	59,00	50,55	64,55
*****	*******	60	164	86	F	08/08/2019	1,78	2,67	66,00	70,11	79,60
*****	*******	61	161	89	F	25/02/2021	1,36	2,44	55,87	56,30	79,42
*****	*******	61	161	89	F	20/05/2021	1,18	1,86	63,53	48,79	60,53
*****	*******	62	161	89	F	12/08/2021	1,34	2,50	53,36	55,85	82,37
*****	*******	62	161	89	F	04/11/2021	1,50	2,31	65,00	62,87	76,13
*****	*******	62	161	89	F	27/01/2022	1,38	2,39	57,99	57,89	78,57
*****	*******	62	161	89	F	28/04/2022	1,53	2,66	57,32	63,78	87,58
*****	*******	63	161	89	F	13/10/2022	1,54	2,71	56,93	65,33	90,15
*****	*******	63	161	89	F	05/01/2023	1,30	2,22	58,67	55,10	73,78
*****	*******	63	161	89	F	30/03/2023	1,32	2,25	58,46	55,68	74,82
*****	*******	63	161	89	F	22/06/2023	1,40	2,68	52,06	59,14	89,23
*****	*******	64	161	89	F	07/12/2023	1,47	2,63	56,05	63,06	88,24
*****	*******	57	164	109	F	19/11/2018	1,48	2,26	65,00	56,53	66,72
*****	*******	57	164	110	F	17/12/2018	1,56	2,24	69,00	59,58	66,07
*****	*******	57	164	110	F	14/01/2019	1,70	2,44	69,00	65,47	71,83
*****	*******	57	164	110	F	11/02/2019	1,64	2,22	73,00	63,24	65,51
*****	*******	57	164	115	F	08/05/2019	1,65	2,30	71,00	63,86	67,97
*****	*******	57	164	114	F	05/08/2019	1,65	2,28	72,00	63,66	67,33
*****	*******	45	175	83	M	09/11/2015	2,85	4,81	59,00	72,18	93,43
*****	*******	45	175	83	M	11/02/2016	2,67	4,32	61,00	67,48	83,85
*****	*******	45	175	83	M	25/05/2016	2,76	4,77	57,00	69,94	92,68
*****	*******	46	175	83	M	08/09/2016	2,51	4,55	55,00	64,12	88,62
*****	*******	46	175	83	M	09/12/2016	2,88	4,70	61,00	73,47	91,53
*****	*******	46	175	82	M	01/03/2017	2,78	4,52	61,00	70,85	88,03
*****	*******	46	175	82	M	25/05/2017	2,77	4,66	59,00	70,68	90,77
*****	*******	47	175	83	M	29/08/2017	2,58	4,38	58,00	66,06	85,50
*****	*******	47	175	83	M	23/11/2017	2,98	4,67	63,00	76,59	91,37
*****	*******	47	175	83	M	05/04/2018	2,85	4,48	63,00	73,31	87,59
*****	*******	47	175	86	M	31/05/2018	2,39	4,13	57,00	61,64	81,03
*****	*******	48	175	84	M	23/08/2018	2,72	4,51	60,00	70,11	88,51
*****	*******	48	175	84	M	20/12/2018	2,79	4,63	60,00	72,05	90,74
*****	*******	48	175	84	M	21/03/2019	2,34	4,35	53,00	60,38	85,43
*****	*******	49	175	83	M	20/06/2019	2,95	4,61	63,00	76,44	90,55
*****	*******	49	175	84	M	19/09/2019	2,69	4,37	61,00	69,76	85,94
*****	*******	50	179	84	M	14/01/2021	2,42	3,61	67,14	60,72	71,18
*****	*******	50	179	84	M	18/03/2021	2,59	4,36	59,48	64,92	85,91
*****	*******	51	179	84	M	10/06/2021	2,80	4,42	63,31	70,72	87,76
*****	*******	51	179	84	M	16/09/2021	2,70	4,50	60,14	68,31	89,24
*****	*******	51	179	84	M	16/12/2021	2,63	3,98	65,99	66,36	79,00
*****	*******	51	179	84	M	10/03/2022	2,59	4,27	60,50	65,30	84,80
*****	*******	51	179	84	M	02/06/2022	2,66	4,38	60,78	67,29	86,98
*****	*******	52	179	84	M	27/10/2022	2,41	3,74	64,36	61,31	74,72
*****	*******	52	179	84	M	26/01/2023	2,63	4,42	59,57	67,01	88,24

*****	*******	52	179	84	M	18/05/2023	2,82	3,60	78,22	71,79	71,99
*****	*******	53	179	84	M	24/08/2023	2,26	3,79	59,66	58,12	76,26
*****	*******	53	179	84	M	09/11/2023	2,45	4,17	58,75	62,91	83,83
*****	*******	53	179	84	M	01/02/2024	2,41	4,21	57,25	61,96	84,72
*****	*******	55	162	75	M	13/11/2017	1,77	3,13	56,46	57,67	81,19
*****	*******	55	162	74	M	13/11/2017	1,42	2,68	52,00	46,32	65,17
*****	*******	55	162	74	M	13/12/2017	1,32	2,53	52,00	43,02	61,66
*****	*******	55	162	74	M	09/01/2018	1,36	2,61	52,00	44,27	63,49
*****	*******	56	162	72	M	03/04/2018	1,49	2,75	54,00	48,81	67,16
*****	*******	56	162	72	M	29/06/2018	1,73	2,81	61,00	56,43	68,44
*****	*******	56	162	75	M	25/09/2018	0,94	2,15	43,00	30,74	52,32
*****	*******	56	162	74	M	19/12/2018	0,95	2,06	46,00	31,09	50,30
*****	*******	57	162	71	M	18/03/2019	1,09	2,30	47,00	35,79	56,21
*****	*******	57	162	72	M	14/06/2019	1,05	2,26	46,00	34,59	55,28
*****	*******	57	162	72	M	05/09/2019	1,03	2,35	43,00	33,91	57,59
*****	*******	58	162	75	M	15/10/2020	1,02	2,29	44,37	34,17	60,86
*****	*******	58	162	75	M	14/01/2021	1,24	2,37	52,18	41,54	62,90
*****	*******	59	160	93	F	16/11/2015	2,18	2,56	85,00	92,04	80,37
*****	*******	59	160	94	F	18/02/2016	1,52	1,77	85,00	64,14	55,52
*****	*******	59	160	88	F	18/05/2016	1,69	2,03	83,00	71,25	63,60
*****	*******	60	160	86	F	16/09/2016	1,88	2,33	80,00	80,39	73,45
*****	*******	60	160	89	F	16/12/2016	2,11	2,40	87,00	90,21	75,82
*****	*******	60	160	88	F	16/03/2017	1,90	2,29	82,00	81,11	72,24
*****	*******	60	160	87	F	16/06/2017	2,21	2,62	84,00	94,61	82,56
*****	*******	61	160	92	F	19/10/2017	2,32	2,73	84,00	97,63	86,63
*****	*******	61	160	92	F	21/12/2017	2,22	2,70	82,00	93,38	85,65
*****	*******	61	160	92	F	15/03/2018	2,04	2,43	83,00	85,91	77,52
*****	*******	61	160	92	F	07/06/2018	1,64	2,06	79,00	69,14	65,75
*****	*******	62	160	89	F	15/11/2018	2,49	2,90	85,00	105,93	92,64
*****	*******	62	160	88	F	28/02/2019	1,99	2,42	82,00	84,49	77,67
*****	*******	62	160	90	F	23/05/2019	2,24	2,71	82,00	95,80	86,95
*****	*******	62	160	91	F	29/07/2019	1,83	2,24	81,00	78,24	72,05
*****	*******	62	160	93	F	02/09/2019	2,37	2,72	87,00	101,93	87,48
*****	*******	63	160	94	F	01/10/2019	2,45	2,86	85,00	105,11	91,94
*****	*******	64	161	95	F	17/09/2020	2,56	3,04	84,26	109,78	102,19
*****	*******	64	161	95	F	25/02/2021	2,29	2,74	83,75	98,22	91,98
*****	*******	64	161	95	F	22/04/2021	2,26	2,68	84,47	96,97	90,04
*****	*******	64	161	95	F	19/08/2021	1,92	2,56	74,90	82,11	85,99
*****	*******	65	161	95	F	09/12/2021	2,38	2,85	83,70	103,27	96,65
*****	*******	65	161	95	F	31/03/2022	2,05	2,42	84,61	88,74	82,16
*****	*******	65	161	95	F	26/05/2022	2,33	2,75	84,74	101,03	93,40
*****	*******	66	161	95	F	15/09/2022	2,31	2,73	84,66	101,55	93,81
*****	*******	66	161	95	F	05/01/2023	1,71	2,55	67,24	75,24	87,50
*****	*******	66	161	95	F	27/04/2023	1,83	2,20	82,86	80,13	75,63
*****	*******	66	161	95	F	24/08/2023	2,27	2,71	83,94	99,77	92,96
*****	*******	67	161	95	F	14/12/2023	1,64	2,00	81,96	72,81	69,33
*****	*******	58	160	53	F	16/09/2015	1,51	3,02	50,00	63,02	93,87
*****	*******	58	160	55	F	10/12/2015	1,47	2,03	72,00	61,66	62,98
*****	*******	58	160	56	F	07/03/2016	1,00	1,33	75,00	41,64	41,23
*****	*******	58	160	55	F	20/04/2016	1,01	2,14	47,00	42,34	66,48
*****	*******	59	160	54	F	25/07/2016	1,29	1,70	75,00	54,44	53,37
*****	*******	59	160	53	F	13/10/2016	1,21	1,83	66,00	50,95	57,47
*****	*******	59	160	54	F	10/11/2016	1,71	3,06	55,00	72,30	96,06
*****	*******	59	160	51	F	08/03/2017	1,38	1,55	89,00	58,40	48,61
*****	*******	60	159	50	F	10/08/2017	1,59	2,67	59,00	66,82	85,73
*****	*******	60	160	51	F	02/11/2017	1,69	2,65	63,00	70,44	83,89
*****	*******	60	159	47	F	25/01/2018	1,10	1,56	70,00	46,67	50,14
*****	*******	60	160	50	F	19/04/2018	0,71	1,40	50,00	29,57	44,43
*****	*******	61	159	47	F	12/07/2018	1,19	1,84	64,00	50,63	59,31
*****	*******	61	160	59	F	18/10/2018					
*****	*******	61	160	59	F	15/11/2018	1,09	2,14	50,00	46,05	68,16
*****	*******	61	159	58	F	07/02/2019	1,46	2,47	59,00	62,18	79,99
*****	*******	61	159	58	F	04/04/2019	1,32	2,53	52,00	56,72	81,95
*****	*******	62	160	61	F	11/07/2019	1,23	1,89	65,00	51,93	60,26
*****	*******	62	159	59	F	10/10/2019	0,94	1,87	50,00	40,33	60,85
*****	*******	63	160	62	F	17/09/2020	1,02	1,29	79,14	43,87	43,61
*****	*******	63	160	62	F	10/12/2020	1,07	1,90	56,16	45,69	63,99
*****	*******	63	160	62	F	25/02/2021	0,84	1,18	70,74	35,87	39,88
*****	*******	64	160	62	F	20/05/2021	0,99	1,97	50,37	42,98	67,02
*****	*******	64	160	62	F	23/12/2021	0,81	2,03	40,19	35,35	69,08

*****	*******	65	160	62	F	04/08/2022	1,48	2,64	55,90	64,90	91,04
*****	*******	65	160	62	F	27/10/2022	1,06	1,95	54,17	46,50	67,31
*****	*******	65	160	62	F	19/01/2023	1,42	2,20	64,48	62,22	75,66
*****	*******	65	160	62	F	16/02/2023	1,30	2,54	51,13	56,99	87,40
*****	*******	65	160	62	F	02/03/2023	1,24	2,13	58,30	54,57	73,39
*****	*******	65	160	62	F	30/03/2023	0,93	1,70	55,08	41,00	58,37
*****	*******	65	160	62	F	13/04/2023	1,10	1,81	60,56	48,23	62,45
*****	*******	66	160	62	F	25/05/2023	1,22	2,07	58,83	54,13	72,02
*****	*******	66	160	62	F	22/06/2023	1,55	2,81	55,38	69,12	97,69
*****	*******	66	160	62	F	20/07/2023	1,28	2,79	45,76	56,71	97,01
*****	*******	66	160	62	F	17/08/2023	0,94	2,38	39,57	41,92	82,92
*****	*******	66	160	62	F	09/11/2023	1,09	2,35	46,32	48,48	81,92
*****	*******	66	160	62	F	01/02/2024	1,03	1,82	56,95	46,00	63,23
*****	*******	63	149	84	M	15/12/2014	2,30	3,26	70,64	97,93	110,19
*****	*******	63	149	84	M	17/12/2014	2,53	4,29	59,01	107,78	145,16
*****	*******	63	149	84	M	17/12/2014	2,01	4,16	48,23	85,42	140,76
*****	*******	63	149	84	M	07/01/2015	1,68	2,67	62,99	71,52	90,26
*****	*******	63	149	84	M	12/01/2015	2,06	3,24	63,70	87,76	109,51
*****	*******	63	149	84	M	26/01/2015	2,53	4,17	60,58	107,64	141,23
*****	*******	63	149	84	M	28/01/2015	2,38	3,55	67,03	101,23	120,05
*****	*******	64	147	83	F	23/11/2015	1,65	2,21	74,00	90,15	88,27
*****	*******	64	147	86	F	29/02/2016	1,68	2,30	73,00	91,72	92,09
*****	*******	64	147	86	F	30/05/2016	1,81	2,64	68,00	99,10	105,50
*****	*******	64	147	85	F	29/08/2016	1,75	2,39	73,00	95,52	95,48
*****	*******	65	147	87	F	21/11/2016	1,81	2,45	73,00	100,45	98,83
*****	*******	65	147	84	F	13/02/2017	1,73	2,46	70,00	96,16	99,09
*****	*******	65	147	87	F	22/05/2017	1,77	2,42	73,00	98,40	97,68
*****	*******	65	147	87	F	24/07/2017	1,70	2,24	75,00	90,21	90,98
*****	*******	65	147	86	F	25/09/2017	1,68	2,28	73,00	89,18	92,50
*****	*******	66	147	86	F	25/01/2018	1,65	2,33	70,00	88,36	94,93
*****	*******	66	147	86	F	19/04/2018	1,68	2,29	73,00	89,76	93,49
*****	*******	66	147	83	F	19/07/2018	1,80	2,47	72,00	96,83	101,11
*****	*******	66	147	82	F	25/10/2018	1,66	2,22	74,00	89,47	91,03
*****	*******	67	147	82	F	24/01/2019	1,60	2,28	70,00	86,40	94,02
*****	*******	67	147	82	F	02/05/2019	1,66	2,23	74,00	90,11	91,77
*****	*******	67	147	82	F	25/07/2019	1,75	2,35	74,00	95,37	97,13
*****	*******	67	147	82	F	31/10/2019	1,61	2,21	72,00	88,07	91,55
*****	*******	68	149	84	M	24/09/2020	1,69	2,27	74,20	75,86	80,42
*****	*******	69	149	84	M	04/03/2021	1,65	2,30	71,81	75,19	82,16
*****	*******	70	149	84	M	23/12/2021	1,56	2,25	69,17	71,81	81,26
*****	*******	70	149	84	M	17/03/2022	1,53	2,20	69,84	70,64	79,17
*****	*******	71	149	84	M	01/12/2022	1,53	2,21	69,19	71,16	80,34
*****	*******	71	149	84	M	23/02/2023	1,45	2,27	64,02	67,58	82,44
*****	*******	71	149	84	M	18/05/2023	1,47	2,21	66,63	68,47	80,27
*****	*******	71	149	84	M	17/08/2023	1,53	2,17	70,58	71,44	79,06
*****	*******	48	169	75	M	28/09/2015	1,84	3,72	49,00	51,37	79,13
*****	*******	48	169	77	M	05/01/2016	2,56	4,05	63,00	71,42	86,09
*****	*******	49	169	78	M	25/04/2016	1,54	3,23	47,00	43,38	69,07
*****	*******	49	169	78	M	08/07/2016	2,55	4,34	58,00	71,72	92,83
*****	*******	49	169	80	M	04/10/2016	1,45	3,26	44,00	40,64	69,72
*****	*******	49	169	78	M	23/01/2017	1,51	3,60	41,00	42,51	76,84
*****	*******	50	169	78	M	18/04/2017	2,10	3,22	65,00	59,32	69,03
*****	*******	50	169	80	M	10/07/2017	2,21	3,45	64,00	62,58	74,01
*****	*******	50	169	80	M	19/10/2017	2,42	4,06	59,00	68,56	87,10
*****	*******	50	169	79	M	08/02/2018	2,19	3,91	56,00	62,35	83,94
*****	*******	51	169	79	M	05/04/2018	1,63	3,17	51,00	46,23	68,22
*****	*******	51	169	79	M	20/09/2018	2,44	4,05	60,00	69,46	87,19
*****	*******	51	169	79	M	14/02/2019	2,51	3,89	64,00	71,61	83,84
*****	*******	52	169	79	M	09/05/2019	2,22	3,61	61,00	63,54	77,76
*****	*******	52	169	79	M	01/08/2019	2,50	3,82	65,00	71,65	82,43
*****	*******	53	169	79	M	10/09/2020	2,65	3,42	77,36	77,23	79,02
*****	*******	53	169	79	M	03/12/2020	2,07	3,07	67,63	60,51	70,81
*****	*******	54	169	79	M	20/05/2021	1,51	3,70	40,79	44,46	86,14
*****	*******	54	169	79	M	18/11/2021	2,70	3,91	69,16	79,60	90,95
*****	*******	54	169	79	M	17/02/2022	2,67	3,42	78,09	78,63	79,57
*****	*******	55	169	79	M	04/08/2022	1,98	2,43	81,52	58,75	56,83
*****	*******	55	169	79	M	27/10/2022	1,78	2,97	60,02	52,90	69,50
*****	*******	55	169	79	M	19/01/2023	1,87	2,63	71,15	55,48	61,48
*****	*******	56	169	79	M	13/04/2023	1,75	3,15	55,64	52,48	74,22
*****	*******	56	169	79	M	13/07/2023	2,28	2,78	81,85	68,28	65,65

*****	*******	56	169	79	M	05/10/2023	2,01	3,23	62,20	60,20	76,17
*****	*******	58	157	62	F	18/09/2015	1,52	2,56	59,00	65,89	83,08
*****	*******	58	157	60	F	14/12/2015	1,53	2,38	64,00	66,55	77,18
*****	*******	58	157	64	F	22/03/2016	1,32	2,12	62,00	57,45	68,98
*****	*******	59	157	64	F	28/06/2016	1,29	2,15	60,00	56,86	70,12
*****	*******	59	157	66	F	30/09/2016	1,24	2,05	60,00	54,42	66,97
*****	*******	59	157	66	F	23/01/2017	1,27	2,16	58,00	55,98	70,54
*****	*******	60	157	64	F	24/04/2017	1,01	1,84	54,00	44,76	60,52
*****	*******	60	157	64	F	19/07/2017	1,02	1,77	57,00	44,10	58,53
*****	*******	60	157	64	F	19/10/2017	1,22	1,96	62,00	52,96	64,62
*****	*******	60	157	59	F	21/12/2017	1,11	1,93	57,00	48,33	63,90
*****	*******	60	157	59	F	15/02/2018	1,60	2,81	56,00	69,42	93,02
*****	*******	61	157	60	F	10/05/2018	1,44	2,43	59,00	62,70	80,59
*****	*******	61	157	60	F	27/09/2018	1,51	2,58	58,00	66,19	85,82
*****	*******	61	157	59	F	20/12/2018	1,53	2,54	60,00	67,00	84,82
*****	*******	61	157	59	F	28/03/2019	1,29	2,29	56,00	56,96	76,19
*****	*******	62	157	60	F	13/06/2019	1,37	2,17	63,00	60,48	72,72
*****	*******	62	157	60	F	12/09/2019	1,01	1,83	55,00	44,84	61,23
*****	*******	65	155	61	F	21/04/2022	1,10	2,25	48,82	51,62	83,25
*****	*******	65	155	61	F	07/07/2022	1,24	2,30	54,05	58,40	85,07
*****	*******	65	155	61	F	29/09/2022	1,12	2,10	53,38	52,80	77,87
*****	*******	65	155	61	F	22/12/2022	0,90	1,71	52,79	42,30	63,08
*****	*******	65	155	61	F	16/03/2023	1,13	2,12	53,59	53,33	78,34
*****	*******	66	155	61	F	08/06/2023	1,26	2,30	54,94	60,07	85,95
*****	*******	66	155	61	F	31/08/2023	1,28	2,46	52,08	60,94	91,97
*****	*******	66	155	61	F	23/11/2023	1,33	2,12	62,55	63,18	79,40
*****	*******	66	155	61	F	15/02/2024	1,14	1,92	59,37	54,20	71,76
*****	*******	79	155	72	M	19/11/2015	1,25	1,90	65,00	55,87	57,60
*****	*******	79	155	67	M	10/02/2016	1,69	2,49	67,00	75,79	75,72
*****	*******	79	155	67	M	05/05/2016	2,00	2,77	72,00	89,62	84,07
*****	*******	79	155	69	M	01/08/2016	1,94	3,02	64,00	87,10	91,67
*****	*******	79	155	68	M	28/09/2016	1,89	2,63	71,00	84,54	79,83
*****	*******	80	155	70	M	19/12/2016	1,80	2,48	72,00	81,52	75,67
*****	*******	80	155	69	M	13/03/2017	1,46	2,11	69,00	66,11	64,40
*****	*******	80	155	66	M	12/06/2017	1,73	2,25	76,00	78,36	68,59
*****	*******	80	155	67	M	01/09/2017	1,56	2,14	72,00	71,39	65,43
*****	*******	80	153	60	M	06/09/2017	2,18	3,85	56,67	105,87	142,26
*****	*******	80	153	60	M	08/09/2017	2,04	3,53	57,88	99,05	130,31
*****	*******	80	153	60	M	12/09/2017	2,97	3,60	82,53	144,16	133,01
*****	*******	80	153	60	M	14/09/2017	3,52	4,15	84,90	170,92	153,30
*****	*******	81	155	67	M	30/11/2017	0,98	1,80	54,00	44,82	55,23
*****	*******	81	155	67	M	22/02/2018	1,57	2,27	69,00	72,17	69,69
*****	*******	81	155	69	M	10/05/2018	1,63	2,23	73,00	74,84	68,39
*****	*******	81	155	70	M	30/08/2018	1,71	2,17	78,00	78,73	66,92
*****	*******	81	155	70	M	27/09/2018	1,66	2,23	74,00	76,71	68,50
*****	*******	82	155	68	M	21/02/2019	1,58	2,13	74,00	73,22	65,85
*****	*******	82	155	68	M	23/05/2019	1,53	2,08	73,00	70,93	64,28
*****	*******	82	155	68	M	22/08/2019	1,38	1,87	73,00	64,37	57,83
*****	*******	84	153	60	M	07/01/2021	1,46	2,25	64,95	73,77	85,74
*****	*******	84	153	60	M	22/04/2021	1,62	2,34	69,53	82,11	89,16
*****	*******	84	153	60	M	22/07/2021	0,95	1,75	54,23	47,92	66,72
*****	*******	73	157	66	F	25/11/2015	1,53	2,59	59,00	79,85	93,89
*****	*******	73	157	67	F	05/04/2016	1,43	2,34	61,00	74,41	84,96
*****	*******	74	157	63	F	01/12/2016	1,42	2,59	54,00	74,98	94,49
*****	*******	74	157	64	F	03/03/2017	1,26	2,09	60,00	66,16	76,41
*****	*******	74	157	63	F	19/05/2017	1,27	2,07	61,00	66,80	75,67
*****	*******	75	157	59	F	30/06/2017	1,90	3,13	60,85	99,24	125,78
*****	*******	75	157	59	F	30/06/2017	1,55	2,83	54,89	80,87	113,65
*****	*******	75	157	59	F	03/07/2017	1,97	2,47	79,87	102,63	99,10
*****	*******	75	157	59	F	10/07/2017	3,05	3,10	98,55	159,13	124,55
*****	*******	75	157	59	F	14/07/2017	1,87	3,20	58,42	97,41	128,62
*****	*******	75	157	59	F	19/07/2017	1,97	3,02	65,26	102,79	121,48
*****	*******	75	157	59	F	21/07/2017	1,44	2,86	50,42	75,01	114,75
*****	*******	75	157	59	F	28/07/2017	2,28	3,51	65,08	118,91	140,93
*****	*******	75	157	59	F	28/07/2017	1,77	3,27	54,20	92,24	131,26
*****	*******	75	157	59	F	17/08/2017	1,16	1,97	58,00	60,49	72,34
*****	*******	75	157	59	F	16/11/2017	1,17	2,06	56,00	61,13	76,07
*****	*******	75	157	59	F	14/02/2018	1,31	2,65	49,00	68,84	97,80
*****	*******	76	157	59	F	13/09/2018	1,02	2,35	43,00	54,05	87,46
*****	*******	76	157	59	F	10/01/2019	0,98	2,08	47,00	51,87	77,20

*****	*******	76	157	59 F	09/05/2019	0,88	1,73	50,00	47,01	64,41
*****	*******	77	157	57 F	01/08/2019	0,90	2,00	45,00	48,25	74,82
*****	*******	78	157	59 F	08/04/2021	1,07	2,12	50,64	58,31	88,28
*****	*******	80	157	59 F	06/10/2022	0,77	1,89	40,85	43,11	80,62
*****	*******	80	157	59 F	14/04/2023	1,30	2,34	55,41	72,29	99,65
*****	*******	80	157	59 F	11/05/2023	1,09	1,81	60,27	60,89	77,17
*****	*******	81	157	59 F	22/06/2023	1,16	2,25	51,50	65,52	97,00
*****	*******	81	157	59 F	21/09/2023	1,23	2,13	57,97	69,62	91,58
*****	*******	51	155	73 F	16/10/2015	0,75	1,87	40,00	30,95	59,70
*****	*******	51	155	73 F	08/01/2016	0,80	1,98	40,00	33,18	63,15
*****	*******	52	155	70 F	15/04/2016	0,65	1,93	33,00	27,14	62,05
*****	*******	52	155	70 F	08/07/2016	0,92	2,54	36,00	38,80	81,66
*****	*******	52	155	70 F	14/10/2016	1,01	2,07	48,00	42,55	66,72
*****	*******	53	155	71 F	03/02/2017	1,12	2,37	47,00	47,28	76,66
*****	*******	53	155	72 F	17/03/2017	1,31	2,99	43,00	55,30	96,90
*****	*******	53	155	72 F	21/04/2017	1,12	2,64	42,00	47,26	85,34
*****	*******	53	155	71 F	19/05/2017	1,06	2,30	46,00	44,98	74,37
*****	*******	53	155	70 F	16/06/2017	1,03	2,70	38,00	43,65	87,47
*****	*******	53	155	71 F	17/08/2017	0,79	2,11	37,00	32,55	68,57
*****	*******	53	155	71 F	13/11/2017	0,95	2,33	40,00	39,31	75,71
*****	*******	54	155	72 F	16/02/2018	0,82	2,48	33,00	34,27	80,92
*****	*******	54	155	72 F	16/03/2018	0,53	2,07	25,00	22,08	67,49
*****	*******	54	155	73 F	11/05/2018	0,79	2,43	32,00	32,89	79,09
*****	*******	54	155	71 F	06/06/2018	1,06	2,57	41,00	44,08	83,83
*****	*******	54	155	72 F	19/07/2018	1,03	2,67	38,00	43,22	87,16
*****	*******	54	155	71 F	31/08/2018	1,30	3,09	42,00	54,33	101,04
*****	*******	54	155	72 F	26/10/2018	1,54	3,33	46,00	64,56	108,68
*****	*******	54	155	71 F	23/11/2018	1,39	3,55	39,00	57,97	116,44
*****	*******	54	155	71 F	18/01/2019	1,83	3,83	47,00	76,97	125,42
*****	*******	55	155	71 F	22/02/2019	0,81	2,65	30,00	33,99	87,03
*****	*******	55	155	72 F	22/03/2019	1,81	3,81	47,00	75,90	124,82
*****	*******	55	155	73 F	26/04/2019	1,99	3,82	52,00	83,41	125,26
*****	*******	55	155	73 F	21/06/2019	1,51	3,36	44,00	63,79	110,65
*****	*******	55	155	74 F	20/09/2019	1,81	3,64	49,00	76,25	119,59
*****	*******	40	165	84 F	08/01/2016	2,24	2,72	82,00	75,31	71,68
*****	*******	41	165	79 F	01/06/2016	2,48	2,99	82,00	83,77	79,11
*****	*******	41	165	79 F	11/11/2016	2,48	3,05	81,00	83,93	80,62
*****	*******	42	165	80 F	13/02/2017	2,38	2,94	80,00	81,33	78,30
*****	*******	42	165	80 F	23/06/2017	2,11	2,49	84,00	71,97	66,27
*****	*******	42	166	77 F	19/09/2017	3,97	4,73	83,95	127,98	123,84
*****	*******	42	166	77 F	25/09/2017	2,66	3,15	84,53	85,72	82,38
*****	*******	42	166	77 F	11/10/2017	1,98	3,06	64,76	63,85	80,09
*****	*******	42	165	80 F	26/10/2017	2,38	2,94	80,00	78,69	78,57
*****	*******	43	165	74 F	01/03/2018	2,14	2,78	76,00	70,73	74,66
*****	*******	43	165	71 F	03/05/2018	2,25	2,80	80,00	74,81	75,15
*****	*******	43	165	71 F	10/01/2019	2,37	2,92	81,00	79,15	78,43
*****	*******	44	165	74 F	25/04/2019	2,31	2,78	83,00	77,11	74,82
*****	*******	44	165	75 F	12/07/2019	2,34	3,02	77,00	78,63	81,60
*****	*******	44	165	73 F	07/10/2019	2,18	2,59	84,00	73,31	70,04
*****	*******	46	166	77 F	15/04/2021	2,07	2,59	80,15	69,15	69,42
*****	*******	46	166	77 F	11/11/2021	2,23	2,85	78,17	74,29	76,47
*****	*******	46	166	77 F	09/12/2021	2,29	2,88	79,59	76,38	77,21
*****	*******	47	166	77 F	27/01/2022	2,37	2,98	79,61	79,87	80,57
*****	*******	47	166	77 F	19/05/2022	2,25	2,79	80,44	75,67	75,53
*****	*******	47	166	77 F	04/08/2022	2,14	2,69	79,61	72,17	72,79
*****	*******	47	166	77 F	19/01/2023	1,93	2,35	82,36	65,03	63,40
*****	*******	48	166	77 F	26/10/2023	3,89	3,89	100,00	132,02	105,79
*****	*******	49	166	77 F	25/01/2024	2,26	2,85	79,26	77,30	78,01
*****	*******	59	168	77 M	24/02/2016	3,30	4,24	77,00	99,85	94,76
*****	*******	59	168	78 M	22/03/2016	3,44	4,19	82,00	104,39	93,75
*****	*******	59	168	77 M	21/04/2016	3,40	4,17	81,00	103,06	93,28
*****	*******	59	168	77 M	18/07/2016	3,58	4,49	79,00	108,59	100,35
*****	*******	59	168	80 M	17/10/2016	3,25	4,08	79,00	98,50	91,18
*****	*******	60	168	81 M	17/01/2017	3,38	4,16	81,00	102,90	93,46
*****	*******	60	168	80 M	12/04/2017	3,25	4,02	80,00	99,23	90,30
*****	*******	60	168	80 M	05/07/2017	3,15	3,92	80,00	96,19	88,14
*****	*******	60	168	80 M	27/09/2017	3,30	4,03	81,00	101,26	90,81
*****	*******	61	168	80 M	18/01/2018	3,13	3,82	81,00	95,89	86,05
*****	*******	61	168	80 M	15/03/2018	3,18	3,91	81,00	97,91	88,04
*****	*******	61	168	81 M	07/06/2018	3,10	3,82	81,00	95,42	86,33

*****	*******	61	168	82	M	27/09/2018	3,03	3,49	86,00	93,42	78,73
*****	*******	61	168	82	M	20/12/2018	2,94	3,59	81,00	90,77	81,14
*****	*******	62	168	84	M	14/03/2019	2,94	3,60	81,00	90,97	81,50
*****	*******	62	168	84	M	06/06/2019	2,86	3,48	82,00	88,62	78,81
*****	*******	62	168	84	M	26/09/2019	2,75	3,43	80,00	85,49	77,84
*****	*******	63	166	85	M	10/09/2020	2,94	3,66	80,13	98,38	95,55
*****	*******	63	166	85	M	03/12/2020	2,83	3,51	80,76	94,98	91,53
*****	*******	64	166	85	M	25/02/2021	2,95	3,55	83,03	99,87	93,45
*****	*******	64	166	85	M	20/05/2021	2,87	3,46	82,95	97,35	91,17
*****	*******	64	166	85	M	12/08/2021	2,71	3,46	78,26	91,75	91,08
*****	*******	64	166	85	M	21/10/2021	2,65	3,15	84,38	89,94	82,80
*****	*******	65	166	85	M	13/01/2022	2,64	3,25	81,31	90,46	86,26
*****	*******	65	166	85	M	21/04/2022	2,74	3,42	80,20	93,80	90,68
*****	*******	65	166	85	M	14/07/2022	2,63	3,35	78,53	89,99	88,86
*****	*******	68	151	48	F	22/10/2015	1,30	2,43	53,00	70,81	94,39
*****	*******	69	151	49	F	05/05/2016	1,39	2,33	59,00	76,60	91,27
*****	*******	69	150	47	F	03/06/2016	2,41	3,96	60,79	127,55	164,84
*****	*******	69	150	47	F	05/07/2016	2,80	3,45	81,10	148,22	143,58
*****	*******	69	151	48	F	14/07/2016	1,42	2,69	52,00	78,06	105,64
*****	*******	69	150	47	F	26/08/2016	2,64	4,32	61,14	139,90	179,77
*****	*******	69	151	48	F	19/09/2016	1,26	2,18	57,00	68,68	84,74
*****	*******	69	151	49	F	14/10/2016	1,19	2,13	55,00	65,30	82,83
*****	*******	69	151	49	F	13/01/2017	1,33	2,32	57,00	72,69	90,26
*****	*******	69	151	48	F	11/04/2017	1,38	2,22	62,00	75,22	86,46
*****	*******	70	151	49	F	05/07/2017	1,35	2,24	60,00	74,47	88,00
*****	*******	70	151	49	F	30/10/2017	1,23	2,26	54,00	65,34	88,82
*****	*******	70	151	49	F	22/02/2018	1,18	2,14	55,00	63,24	84,32
*****	*******	71	151	49	F	18/07/2018	1,28	2,23	57,00	68,59	88,19
*****	*******	71	151	48	F	24/10/2018	1,19	2,19	54,00	64,47	86,83
*****	*******	71	151	48	F	28/02/2019	1,27	2,32	54,00	68,79	92,54
*****	*******	72	151	48	F	02/05/2019	1,26	2,32	54,00	68,29	92,35
*****	*******	72	151	48	F	22/08/2019	1,23	2,22	55,00	67,35	88,90
*****	*******	73	150	47	F	29/04/2021	1,32	2,38	55,67	73,93	103,54
*****	*******	74	150	47	F	30/12/2021	1,21	2,44	49,65	68,63	107,54
*****	*******	74	150	47	F	24/03/2022	1,22	2,23	54,88	69,22	98,11
*****	*******	75	150	47	F	16/06/2022	1,19	2,44	48,56	68,03	108,75
*****	*******	76	150	47	F	18/08/2023	1,20	2,46	48,58	69,54	110,94
*****	*******	49	156	138	F	03/02/2016	1,79	2,06	86,00	71,82	63,96
*****	*******	49	156	126	F	03/06/2016	1,62	1,86	87,00	65,12	57,85
*****	*******	49	156	98	F	14/10/2016	2,19	2,51	87,00	88,00	77,99
*****	*******	50	156	84	F	03/05/2017	2,55	3,01	84,00	103,09	93,92
*****	*******	50	156	84	F	05/10/2017	2,35	2,90	81,00	93,17	91,01
*****	*******	51	156	75	F	08/03/2018	2,48	3,03	81,00	98,94	95,28
*****	*******	51	156	78	F	26/07/2018	2,36	2,76	85,00	94,21	87,22
*****	*******	51	156	80	F	22/11/2018	2,42	2,97	81,00	97,22	93,86
*****	*******	52	156	81	F	21/02/2019	2,66	3,04	87,00	107,36	96,16
*****	*******	52	156	86	F	13/06/2019	2,56	3,07	83,00	103,14	97,50
*****	*******	52	156	87	F	12/09/2019	2,35	2,71	86,00	95,10	86,05
*****	*******	53	156	92	F	10/12/2020	2,43	2,85	85,12	98,55	92,83
*****	*******	54	156	92	F	25/03/2021	2,41	2,80	86,10	98,91	91,92
*****	*******	54	156	92	F	25/11/2021	2,51	2,99	83,94	102,92	98,12
*****	*******	55	156	92	F	03/03/2022	2,48	3,03	81,85	102,56	100,13
*****	*******	55	156	92	F	01/09/2022	2,43	2,87	84,81	100,82	95,00
*****	*******	56	156	92	F	03/11/2023	2,48	2,94	84,60	103,94	98,01
*****	*******	48	163	95	F	08/10/2015	2,74	3,32	82,00	99,86	93,21
*****	*******	48	163	95	F	29/12/2015	2,12	2,59	81,00	77,35	72,65
*****	*******	48	163	93	F	11/04/2016	2,27	2,58	87,00	82,96	72,44
*****	*******	49	163	95	F	05/07/2016	2,27	2,68	84,00	83,94	75,79
*****	*******	49	163	98	F	07/10/2016					
*****	*******	49	163	98	F	07/10/2016	2,41	2,86	84,00	88,75	80,85
*****	*******	49	163	101	F	07/04/2017	2,06	2,46	83,00	76,19	69,60
*****	*******	50	163	100	F	17/07/2017	2,22	2,68	82,00	79,87	76,19
*****	*******	50	164	100	F	31/10/2017	2,15	2,79	77,00	76,40	78,23
*****	*******	51	157	70	F	12/08/2015	4,04	5,05	80,02	158,73	159,41
*****	*******	51	156	84	F	03/09/2015	2,13	4,09	52,00	87,28	128,59
*****	*******	51	156	81	F	03/12/2015	2,32	4,62	50,00	95,23	145,33
*****	*******	51	156	83	F	10/03/2016	2,24	4,28	52,00	91,89	134,52
*****	*******	52	156	84	F	08/06/2016	2,18	4,40	49,00	90,26	139,28
*****	*******	52	156	85	F	08/09/2016	2,23	4,26	52,00	92,01	134,83
*****	*******	52	156	83	F	01/12/2016	2,26	4,51	50,00	93,42	142,71

*****	*******	52	156	84	F	02/03/2017	2,39	4,37	54,00	98,62	138,45
*****	*******	52	156	81	F	25/05/2017	2,39	4,64	51,00	98,79	146,99
*****	*******	53	156	83	F	31/08/2017	2,41	4,49	53,00	97,99	143,49
*****	*******	53	156	83	F	30/11/2017	2,22	4,50	49,00	90,74	143,68
*****	*******	53	156	84	F	22/02/2018	2,43	4,28	56,00	99,08	137,22
*****	*******	53	156	84	F	24/05/2018	2,18	4,22	51,00	89,25	135,16
*****	*******	54	156	84	F	27/09/2018	2,36	4,40	53,00	96,94	141,49
*****	*******	54	156	84	F	07/02/2019	2,32	4,34	53,00	95,94	140,05
*****	*******	54	156	80	F	02/05/2019	2,08	4,26	48,00	86,11	137,40
*****	*******	55	156	80	F	22/08/2019	2,55	4,56	55,00	106,01	147,49
*****	*******	56	157	70	F	24/09/2020	2,53	4,66	54,23	104,38	153,46
*****	*******	56	157	70	F	22/12/2020	2,42	4,43	54,57	99,81	145,83
*****	*******	56	157	70	F	31/03/2021	2,34	4,26	55,01	96,64	140,07
*****	*******	57	157	70	F	05/08/2021	2,21	4,39	50,41	92,39	145,84
*****	*******	57	157	70	F	28/10/2021	2,26	4,49	50,36	94,38	149,14
*****	*******	57	157	70	F	26/05/2022	2,55	4,34	58,86	106,52	144,04
*****	*******	58	157	70	F	18/08/2022	2,33	4,05	57,63	98,31	135,60
*****	*******	58	157	70	F	09/02/2023	2,33	4,31	53,91	98,07	144,60
*****	*******	58	157	70	F	04/05/2023	2,51	4,08	61,60	105,99	136,77
*****	*******	59	157	70	F	20/07/2023	2,46	4,34	56,72	104,96	146,85
*****	*******	59	157	70	F	26/10/2023	2,15	4,11	52,32	91,71	139,12
*****	*******	59	157	70	F	18/01/2024	2,47	4,20	58,73	105,22	142,19
*****	*******	69	163	81	F	13/10/2015	0,99	2,45	40,00	44,94	79,01
*****	*******	69	163	73	F	13/01/2016	0,83	2,44	34,00	37,61	78,73
*****	*******	69	163	74	F	11/04/2016	1,02	2,56	39,00	46,26	82,74
*****	*******	70	163	74	F	07/07/2016	1,17	2,56	45,00	53,96	83,26
*****	*******	70	163	78	F	13/10/2016	1,07	2,43	44,00	49,25	79,00
*****	*******	70	163	82	F	07/04/2017	1,08	2,28	47,00	49,92	74,13
*****	*******	71	163	86	F	10/07/2017	1,07	2,15	49,00	49,04	70,54
*****	*******	71	163	86	F	09/11/2017	0,94	2,21	42,00	43,50	72,36
*****	*******	71	163	91	F	19/04/2018	1,02	2,16	47,00	47,34	71,08
*****	*******	72	163	89	F	13/09/2018	0,85	1,98	42,00	39,51	65,21
*****	*******	72	163	89	F	15/11/2018	0,83	1,38	60,00	38,64	45,77
*****	*******	72	163	89	F	21/02/2019	1,04	2,05	50,00	48,62	68,03
*****	*******	72	163	89	F	23/05/2019	0,98	2,25	43,00	46,18	74,65
*****	*******	73	163	89	F	01/07/2019	0,83	1,94	42,00	39,04	64,47
*****	*******	73	163	92	F	13/08/2019	0,77	1,70	45,00	36,55	56,57
*****	*******	73	163	90	F	06/09/2019	0,82	1,73	47,00	38,68	57,61
*****	*******	73	163	90	F	06/09/2019	0,00	0,00		0,00	0,00
*****	*******	73	163	91	F	04/10/2019	0,72	1,48	48,00	34,30	49,15
*****	*******	74	162	95	F	06/05/2021	0,87	1,94	44,92	41,86	71,73
*****	*******	75	162	95	F	05/08/2021	0,59	1,40	41,70	28,53	52,53
*****	*******	75	162	95	F	23/09/2021	0,82	1,20	68,77	40,16	44,85
*****	*******	75	162	95	F	23/12/2021	0,82	2,04	40,23	39,99	76,32
*****	*******	75	162	95	F	20/01/2022	0,81	1,32	60,97	39,36	49,58
*****	*******	75	162	95	F	17/02/2022	0,70	1,95	36,06	34,22	72,88
*****	*******	75	162	95	F	17/03/2022	0,75	2,05	36,77	36,73	76,71
*****	*******	76	162	95	F	16/06/2022	0,72	1,95	36,64	35,39	74,04
*****	*******	76	162	95	F	08/09/2022	0,74	1,75	42,40	36,69	66,34
*****	*******	76	162	95	F	01/12/2022	0,73	1,58	46,43	36,21	59,79
*****	*******	76	162	95	F	05/01/2023	0,74	1,64	45,03	36,44	62,03
*****	*******	76	162	95	F	19/01/2023	0,71	1,45	49,02	35,04	54,80
*****	*******	76	162	95	F	02/02/2023	0,71	1,83	38,75	35,10	69,43
*****	*******	76	162	95	F	16/02/2023	0,62	1,73	35,53	30,40	65,60
*****	*******	76	162	95	F	02/03/2023	0,72	1,49	48,38	35,57	56,38
*****	*******	76	162	95	F	30/03/2023	0,77	1,55	49,73	37,99	58,56
*****	*******	76	162	95	F	13/04/2023	0,72	1,70	42,63	35,74	64,27
*****	*******	76	162	95	F	01/06/2023	0,80	1,12	70,68	39,28	42,61
*****	*******	77	162	95	F	29/06/2023	0,79	1,71	46,54	39,74	65,34
*****	*******	77	162	95	F	25/01/2024	0,77	1,88	41,07	38,60	71,90
*****	*******	41	169	108	M	23/09/2015	2,82	3,96	71,00	75,53	82,51
*****	*******	41	169	112	M	21/12/2015	2,83	4,06	69,00	75,83	84,52
*****	*******	41	169	113	M	29/03/2016	2,29	3,44	66,00	61,42	71,62
*****	*******	41	169	106	M	14/07/2016	2,63	4,33	60,00	70,46	90,11
*****	*******	42	169	100	M	26/01/2017	2,85	4,08	69,00	76,76	85,12
*****	*******	42	169	104	M	20/04/2017	2,78	4,09	67,00	74,82	85,35
*****	*******	43	169	100	M	14/12/2017	2,67	4,24	62,00	72,42	88,88
*****	*******	43	169	105	M	26/04/2018	3,11	4,23	73,00	84,84	88,78
*****	*******	43	169	106	M	12/07/2018	3,02	4,29	70,00	82,31	90,20
*****	*******	46	169	66	F	29/03/2017	2,79	3,71	75,00	93,74	95,55

*****	*******	47	169	64	F	25/04/2017	2,71	3,83	70,00	92,01	99,11
*****	*******	47	169	66	F	09/05/2017	2,55	3,72	68,00	86,35	96,35
*****	*******	47	170	65	F	06/06/2017	2,84	3,86	73,00	95,36	99,04
*****	*******	47	170	64	F	03/07/2017	2,82	3,92	71,00	94,57	100,48
*****	*******	47	170	64	F	31/07/2017	2,66	3,63	73,00	85,14	93,36
*****	*******	47	170	66	F	26/09/2017	2,59	3,50	74,00	83,20	89,95
*****	*******	47	170	65	F	28/12/2017	2,72	3,54	76,00	87,59	91,01
*****	*******	47	170	65	F	22/03/2018	2,70	3,63	74,00	87,09	93,61
*****	*******	48	170	65	F	27/06/2018	2,63	3,57	73,00	85,24	91,99
*****	*******	48	170	68	F	28/08/2018	2,77	3,42	80,00	89,53	88,35
*****	*******	48	170	69	F	27/12/2018	2,09	3,19	65,00	67,98	82,35
*****	*******	48	170	69	F	27/12/2018	1,88	2,83	66,00	61,05	73,16
*****	*******	48	170	71	F	26/02/2019	2,35	3,38	69,00	76,46	87,65
*****	*******	49	170	68	F	05/07/2019	2,69	3,60	74,00	88,01	93,63
*****	*******	49	170	70	F	07/10/2019	2,43	3,33	72,00	79,51	86,50
*****	*******	65	161	66	F	18/09/2017	0,50	0,56	89,00	21,84	18,21
*****	*******	65	161	71	F	02/03/2018	0,38	0,45	84,00	16,87	14,64
*****	*******	65	161	71	F	03/04/2018	0,42	0,46	91,00	18,37	15,01
*****	*******	66	161	72	F	03/05/2018	0,43	0,49	87,00	19,01	15,91
*****	*******	66	161	71	F	04/06/2018	0,44	0,48	91,00	19,29	15,48
*****	*******	66	161	71	F	06/09/2018	0,52	0,59	88,00	22,76	19,02
*****	*******	66	161	75	F	03/01/2019	0,41	0,50	82,00	18,24	16,27
*****	*******	67	161	71	F	17/05/2019	0,45	0,52	86,00	20,18	16,99
*****	*******	67	161	71	F	19/08/2019	0,48	0,56	85,00	21,53	18,32
*****	*******	68	143	59	F	18/09/2015	2,54	3,65	69,56	147,06	167,57
*****	*******	68	143	59	F	14/10/2015	2,28	3,78	60,32	132,09	173,57
*****	*******	70	147	65	F	09/06/2017	0,61	0,91	67,00	36,23	38,25
*****	*******	70	147	66	F	16/10/2017	0,96	1,35	71,00	53,96	57,52
*****	*******	70	147	66	F	15/11/2017	1,33	1,73	76,00	75,60	73,81
*****	*******	70	147	66	F	13/12/2017	1,13	1,46	77,00	64,32	62,27
*****	*******	71	147	66	F	15/02/2018	1,30	1,58	82,00	73,77	67,25
*****	*******	71	147	66	F	15/03/2018	1,32	1,68	78,00	75,27	71,51
*****	*******	71	147	66	F	08/06/2018	1,48	1,81	81,00	84,30	77,28
*****	*******	71	147	66	F	13/09/2018	1,49	1,84	80,00	85,90	78,48
*****	*******	71	147	65	F	05/12/2018	1,41	1,71	82,00	80,82	73,54
*****	*******	72	147	65	F	07/03/2019	1,47	1,87	78,00	85,00	80,21
*****	*******	72	147	64	F	06/06/2019	1,47	1,76	83,00	84,98	75,65
*****	*******	72	147	64	F	05/09/2019	1,31	1,63	80,00	76,44	70,20
*****	*******	73	143	59	F	24/09/2020	1,24	1,66	74,69	76,74	80,65
*****	*******	73	143	59	F	22/12/2020	1,34	1,76	76,20	82,79	85,28
*****	*******	74	143	59	F	18/03/2021	1,31	1,76	74,38	81,88	86,26
*****	*******	74	143	59	F	17/06/2021	1,37	1,84	74,80	86,10	90,18
*****	*******	74	143	59	F	02/12/2021	1,17	1,77	66,10	73,38	86,98
*****	*******	75	143	59	F	24/02/2022	1,18	1,51	78,26	75,25	75,15
*****	*******	75	143	59	F	15/09/2022	1,10	1,49	73,56	69,60	73,95
*****	*******	69	150	52	F	01/10/2015	1,16	1,69	68,00	64,41	66,69
*****	*******	69	150	52	F	21/12/2015	0,84	1,30	64,00	46,78	51,34
*****	*******	69	150	52	F	23/06/2016	1,08	1,64	65,00	60,13	64,72
*****	*******	70	150	52	F	21/09/2016	1,10	1,70	64,00	61,97	67,80
*****	*******	70	150	53	F	15/12/2016	1,13	1,80	62,00	63,22	71,75
*****	*******	70	150	54	F	08/03/2017	1,10	1,58	69,00	61,75	62,79
*****	*******	70	150	53	F	31/05/2017	1,20	1,80	66,00	67,63	71,66
*****	*******	70	150	53	F	17/08/2017	1,02	1,35	75,00	55,44	54,08
*****	*******	71	150	53	F	09/11/2017	0,96	1,40	68,00	52,30	56,64
*****	*******	71	150	50	F	03/05/2018	1,08	1,53	70,00	59,43	61,86
*****	*******	71	150	48	F	26/07/2018	1,25	1,78	70,00	68,64	71,91
*****	*******	72	150	48	F	25/10/2018	0,96	1,32	72,00	53,21	53,73
*****	*******	72	150	48	F	28/02/2019	1,05	1,57	66,00	58,32	63,71
*****	*******	72	150	48	F	30/05/2019	1,06	1,70	62,00	58,89	69,43
*****	*******	73	150	50	F	03/09/2019	0,98	1,30	75,00	54,74	53,21
*****	*******	73	146	46	F	03/09/2020	0,98	1,48	65,96	57,83	68,63
*****	*******	74	146	46	F	14/01/2021	0,84	1,29	65,41	50,69	60,50
*****	*******	74	146	46	F	08/04/2021	0,83	1,41	58,51	49,65	66,25
*****	*******	74	146	46	F	01/07/2021	0,84	1,17	72,15	50,52	54,67
*****	*******	75	146	46	F	23/09/2021	1,92	2,57	74,94	116,91	121,58
*****	*******	76	146	46	F	15/12/2022	0,62	0,93	66,34	38,11	44,68
*****	*******	76	146	46	F	09/03/2023	0,72	1,24	58,15	44,40	59,37
*****	*******	76	146	46	F	01/06/2023	0,62	1,24	50,16	38,28	59,35
*****	*******	75	140	48	F	05/10/2015	1,66	2,35	70,00	125,00	120,73
*****	*******	75	140	51	F	04/02/2016	1,39	2,05	67,00	104,75	105,00

*****	*******	76	140	50	F	04/05/2016	1,57	2,46	63,00	120,01	127,56
*****	*******	76	140	48	F	27/07/2016	1,44	2,36	61,00	109,58	122,17
*****	*******	76	140	50	F	27/10/2016	1,37	2,07	66,00	104,56	107,05
*****	*******	76	140	52	F	18/01/2017	1,37	2,05	66,00	104,90	106,00
*****	*******	77	140	51	F	03/04/2017	1,36	2,04	66,00	105,92	106,98
*****	*******	78	140	52	F	28/05/2018	1,38	2,18	63,00	96,08	115,70
*****	*******	72	175	87	M	28/09/2015	2,06	3,03	67,00	60,82	63,76
*****	*******	72	175	87	M	21/12/2015	1,76	2,54	69,00	52,20	53,51
*****	*******	73	175	89	M	23/03/2016	2,34	2,96	79,00	69,59	62,51
*****	*******	73	175	88	M	20/06/2016	1,71	2,54	67,00	50,94	53,57
*****	*******	73	175	88	M	20/09/2016	1,66	2,74	60,00	49,43	57,90
*****	*******	73	175	88	M	13/12/2016	0,00	0,00		0,00	0,00
*****	*******	74	175	80	M	08/03/2017	2,02	2,72	74,00	60,80	57,56
*****	*******	74	175	82	M	19/06/2017	2,21	3,16	69,00	66,51	67,05
*****	*******	74	175	84	M	19/09/2017	2,47	3,18	77,00	74,31	67,56
*****	*******	74	175	84	M	21/12/2017	2,35	3,26	72,00	71,11	69,18
*****	*******	75	175	84	M	15/03/2018	2,58	3,61	71,00	77,97	76,58
*****	*******	75	175	80	M	19/06/2018	2,39	3,26	73,00	72,41	69,44
*****	*******	75	175	82	M	13/09/2018	2,15	2,84	75,00	65,14	60,53
*****	*******	75	175	82	M	10/01/2019	1,57	2,23	70,00	47,74	47,52
*****	*******	76	175	88	M	02/05/2019	1,74	2,66	65,00	52,81	56,70
*****	*******	76	175	88	M	25/07/2019	1,38	2,05	67,00	41,95	43,81
*****	*******	76	175	86	M	24/10/2019	1,66	2,37	70,00	50,67	50,63
*****	*******	78	167	90	M	31/03/2021	2,15	2,81	76,68	84,13	82,48
*****	*******	78	167	90	M	10/06/2021	2,23	3,27	68,27	87,20	96,03
*****	*******	78	167	90	M	09/09/2021	1,83	2,73	66,86	71,44	80,32
*****	*******	78	167	90	M	02/12/2021	2,00	2,75	72,64	78,01	80,73
*****	*******	54	160	70	F	26/10/2015	2,24	2,78	80,00	89,81	84,13
*****	*******	55	160	70	F	22/01/2016	2,41	2,93	82,00	97,65	89,28
*****	*******	55	160	68	F	25/04/2016	2,08	2,57	80,00	84,25	78,49
*****	*******	55	160	71	F	25/08/2016	1,91	2,47	77,00	77,25	75,45
*****	*******	55	160	68	F	22/11/2016	2,42	3,35	72,00	98,13	102,16
*****	*******	56	160	69	F	20/02/2017	2,21	2,58	85,00	90,54	79,24
*****	*******	56	160	68	F	14/06/2017	1,99	2,46	80,00	81,76	75,53
*****	*******	56	160	70	F	07/09/2017	1,88	2,32	81,00	74,97	71,70
*****	*******	56	160	69	F	30/11/2017	1,93	2,41	80,00	77,38	74,36
*****	*******	57	160	69	F	22/02/2018	2,12	2,53	83,00	85,29	78,46
*****	*******	57	160	66	F	21/05/2018	2,13	2,62	81,00	85,36	81,17
*****	*******	57	160	66	F	18/07/2018	2,16	2,49	86,00	87,28	77,03
*****	*******	57	160	64	F	16/10/2018	2,40	2,76	86,00	96,89	85,71
*****	*******	57	160	64	F	11/01/2019	2,24	2,65	84,00	90,74	82,33
*****	*******	58	160	64	F	07/03/2019	2,00	2,48	80,00	80,86	77,19
*****	*******	58	160	67	F	04/06/2019	2,21	2,53	87,00	89,89	78,97
*****	*******	58	160	68	F	02/09/2019	2,08	2,43	85,00	84,72	76,05
*****	*******	72	154	74	F	03/09/2015	1,44	2,38	60,00	77,57	89,78
*****	*******	72	154	73	F	04/12/2015	1,28	2,31	55,00	69,04	87,09
*****	*******	72	154	71	F	10/03/2016	1,56	2,50	62,00	84,31	94,19
*****	*******	72	154	72	F	10/06/2016	1,40	2,29	61,00	75,84	86,59
*****	*******	73	154	72	F	08/09/2016	1,33	2,09	63,00	72,87	79,49
*****	*******	73	154	71	F	01/12/2016	1,42	2,41	58,00	77,34	91,70
*****	*******	73	154	70	F	02/03/2017	1,52	2,39	63,00	83,04	90,76
*****	*******	73	154	71	F	01/06/2017	1,27	2,16	58,00	69,21	82,13
*****	*******	74	154	72	F	05/09/2017	1,46	2,39	61,00	77,91	91,96
*****	*******	74	154	72	F	30/11/2017	1,40	2,34	59,00	75,30	89,86
*****	*******	74	154	74	F	01/03/2018	1,47	2,41	60,00	79,56	93,09
*****	*******	74	154	73	F	05/07/2018	1,50	2,39	62,00	81,02	92,28
*****	*******	75	154	74	F	04/10/2018	1,51	2,51	60,00	82,10	97,10
*****	*******	75	154	74	F	10/01/2019	1,48	2,35	62,00	80,61	91,22
*****	*******	75	154	74	F	11/04/2019	1,57	2,43	64,00	86,06	94,71
*****	*******	75	154	74	F	04/07/2019	1,54	2,51	61,00	84,61	97,75
*****	*******	76	154	73	F	10/10/2019	1,45	2,31	62,00	80,22	90,37
*****	*******	77	153	58	F	10/09/2020	1,64	2,83	58,12	92,90	123,27
*****	*******	77	153	58	F	10/12/2020	1,68	2,58	65,34	95,12	112,27
*****	*******	77	153	58	F	10/06/2021	1,63	2,84	57,31	91,93	123,69
*****	*******	78	153	58	F	16/09/2021	1,74	2,95	59,05	99,96	130,25
*****	*******	78	153	58	F	23/12/2021	1,61	2,83	57,03	92,51	124,81
*****	*******	78	153	58	F	17/03/2022	1,64	2,89	56,95	94,19	127,25
*****	*******	78	153	58	F	09/06/2022	1,53	2,70	56,75	87,96	119,25
*****	*******	79	153	58	F	08/09/2022	1,59	2,86	55,57	92,20	127,43
*****	*******	79	153	58	F	01/12/2022	1,56	2,61	59,61	90,30	116,36

*****	*******	79	153	58	F	23/02/2023	1,63	2,91	56,11	94,80	129,76
*****	*******	79	153	58	F	18/05/2023	1,59	2,74	57,82	92,17	122,43
*****	*******	79	153	58	F	10/08/2023	1,69	2,99	56,35	97,98	133,55
*****	*******	80	153	58	F	02/11/2023	1,80	3,16	57,06	106,07	142,54
*****	*******	80	153	58	F	25/01/2024	1,74	2,88	60,41	102,16	129,68
*****	*******	44	153	69	F	20/10/2015	2,43	3,13	77,00	96,24	98,01
*****	*******	47	153	70	F	07/02/2018	2,27	3,06	74,00	90,69	97,86
*****	*******	47	153	70	F	26/04/2018	2,49	3,14	79,00	99,83	100,49
*****	*******	47	153	72	F	20/09/2018	2,53	3,22	78,00	101,58	103,22
*****	*******	47	153	72	F	17/10/2018	2,82	3,43	82,00	113,71	110,21
*****	*******	47	153	68	F	14/11/2018	2,67	3,39	78,00	107,57	108,85
*****	*******	47	153	63	F	12/12/2018	2,74	3,41	80,00	110,42	109,55
*****	*******	48	153	63	F	07/03/2019	2,72	3,38	80,00	110,06	108,78
*****	*******	48	153	52	F	08/07/2019	2,95	3,57	82,00	119,40	115,07
*****	*******	48	153	49	F	03/10/2019	2,78	3,29	84,00	113,07	106,48
*****	*******	49	152	63	F	19/11/2020	2,67	3,55	75,07	110,18	118,87
*****	*******	50	152	63	F	13/05/2021	2,50	3,37	74,12	104,13	113,59
*****	*******	50	152	63	F	05/08/2021	2,21	3,21	68,98	92,25	108,13
*****	*******	50	152	63	F	28/10/2021	2,75	3,47	79,18	114,60	117,03
*****	*******	51	152	63	F	27/01/2022	2,17	3,18	68,22	91,41	108,18
*****	*******	52	152	63	F	21/04/2023	2,10	2,98	70,48	89,12	101,91
*****	*******	49	175	90	M	21/12/2016	2,42	3,26	74,11	63,25	67,59
*****	*******	63	175	79	M	08/10/2015	2,09	4,78	43,00	58,58	97,93
*****	*******	63	175	81	M	14/04/2016	1,81	3,96	45,00	50,61	81,19
*****	*******	64	175	83	M	06/07/2016	1,61	3,97	40,00	45,23	81,49
*****	*******	64	175	81	M	23/11/2016	1,38	3,11	44,00	38,89	63,89
*****	*******	64	175	85	M	16/02/2017	1,14	2,71	42,00	32,24	55,54
*****	*******	65	180	84	M	13/06/2017	1,90	3,70	51,00	50,27	71,38
*****	*******	65	180	84	M	05/09/2017	1,59	3,69	43,00	42,04	71,17
*****	*******	65	180	84	M	30/11/2017	2,04	4,76	42,00	54,18	91,71
*****	*******	65	180	84	M	22/03/2018	1,65	4,11	40,00	43,85	79,34
*****	*******	66	180	84	M	14/06/2018	1,67	4,65	35,00	44,55	89,76
*****	*******	66	180	84	M	06/09/2018	1,40	3,32	42,00	37,40	64,27
*****	*******	66	180	84	M	10/01/2019	0,92	2,22	41,00	24,58	42,92
*****	*******	50	163	60	F	02/10/2015	2,20	2,96	74,00	81,78	84,06
*****	*******	51	163	61	F	22/07/2016	2,14	4,23	50,00	80,48	120,95
*****	*******	51	163	63	F	25/08/2016	2,23	3,14	71,00	83,98	89,65
*****	*******	51	163	64	F	26/09/2016	2,13	2,92	72,00	80,01	83,43
*****	*******	51	163	63	F	24/10/2016	1,83	2,91	62,00	68,76	83,11
*****	*******	51	163	62	F	21/11/2016	2,07	2,97	69,00	77,87	84,78
*****	*******	51	163	62	F	16/03/2017	2,04	2,61	78,00	76,83	74,45
*****	*******	52	163	63	F	20/09/2017	1,90	2,71	70,00	69,91	78,22
*****	*******	52	163	63	F	18/12/2017	2,22	3,00	74,00	82,00	86,43
*****	*******	52	163	64	F	22/03/2018	2,37	3,04	77,00	87,63	87,75
*****	*******	53	163	65	F	27/06/2018	1,84	2,61	70,00	68,33	75,65
*****	*******	53	163	66	F	27/09/2018	2,05	2,81	72,00	76,21	81,56
*****	*******	53	163	64	F	25/10/2018	2,25	3,01	74,00	83,56	87,33
*****	*******	53	163	66	F	21/11/2018	2,25	2,97	75,00	83,65	85,96
*****	*******	53	163	66	F	19/12/2018	2,31	2,90	79,00	85,81	84,39
*****	*******	53	163	67	F	11/03/2019	2,21	2,88	76,00	82,40	83,84
*****	*******	54	163	65	F	08/07/2019	2,33	3,04	76,00	87,37	88,51
*****	*******	54	163	65	F	03/10/2019	1,81	2,56	70,00	67,96	74,71
*****	*******	55	158	64	F	10/09/2020	1,68	2,10	80,06	67,72	67,48
*****	*******	55	158	64	F	14/01/2021	1,95	2,70	72,38	78,76	86,81
*****	*******	55	158	64	F	08/04/2021	1,94	2,83	68,48	78,18	91,08
*****	*******	56	158	64	F	17/06/2021	1,93	2,77	69,47	78,47	89,98
*****	*******	56	158	64	F	09/09/2021	1,80	2,65	68,06	73,39	85,89
*****	*******	56	158	64	F	02/12/2021	1,69	2,73	61,90	68,89	88,65
*****	*******	56	158	64	F	24/02/2022	1,77	2,79	63,42	71,93	90,35
*****	*******	57	158	64	F	19/05/2022	2,06	3,03	68,07	84,83	99,09
*****	*******	57	158	64	F	08/09/2022	1,88	2,69	69,74	77,18	88,00
*****	*******	57	158	64	F	24/11/2022	1,92	2,68	71,87	79,18	87,61
*****	*******	57	158	64	F	15/12/2022	2,14	2,95	72,62	88,17	96,55
*****	*******	57	158	64	F	29/12/2022	2,30	3,13	73,52	94,81	102,54
*****	*******	57	158	64	F	12/01/2023	2,28	3,17	71,84	93,72	103,73
*****	*******	57	158	64	F	26/01/2023	2,28	3,09	73,81	93,71	100,95
*****	*******	57	158	64	F	09/02/2023	2,10	3,08	68,07	86,24	100,73
*****	*******	57	158	64	F	09/03/2023	2,22	3,08	72,04	91,18	100,63
*****	*******	57	158	64	F	13/04/2023	2,28	2,99	76,13	93,62	97,78
*****	*******	58	158	64	F	18/05/2023	2,32	3,03	76,47	96,39	100,07

*****	*******	58	158	64 F	15/06/2023	2,37	3,02	78,51	98,67	99,78
*****	*******	58	158	64 F	06/07/2023	2,15	3,00	71,42	89,25	99,21
*****	*******	58	158	64 F	31/08/2023	2,01	2,77	72,79	83,74	91,33
*****	*******	58	158	64 F	23/11/2023	2,13	2,77	76,86	88,48	91,39
*****	*******	58	158	64 F	15/02/2024	2,14	2,93	73,11	88,96	96,60
*****	*******	66	168	66 F	26/11/2015	1,53	2,60	58,00	62,57	76,12
*****	*******	68	168	67 F	08/01/2018	2,03	2,98	68,00	84,09	88,80
*****	*******	68	168	68 F	25/01/2018	2,13	3,01	70,00	87,94	89,65
*****	*******	68	168	68 F	07/02/2018	2,27	3,19	71,00	93,83	94,90
*****	*******	68	168	69 F	07/03/2018	2,36	3,25	72,00	97,55	96,68
*****	*******	68	168	69 F	04/04/2018	2,34	3,11	75,00	96,58	92,68
*****	*******	68	168	67 F	29/05/2018	2,36	3,36	70,00	97,90	100,17
*****	*******	68	168	66 F	18/07/2018	2,34	3,26	71,00	97,28	97,40
*****	*******	69	168	65 F	15/10/2018	2,52	3,35	75,00	104,90	100,11
*****	*******	69	168	65 F	07/01/2019	2,02	2,82	71,00	84,49	84,38
*****	*******	69	168	65 F	02/04/2019	1,91	2,82	67,00	80,07	84,48
*****	*******	69	168	65 F	29/05/2019	1,85	2,72	68,00	77,73	81,72
*****	*******	69	168	65 F	08/08/2019	2,08	3,02	68,00	87,73	90,57
*****	*******	69	168	68 F	13/09/2019	2,05	2,89	70,00	86,51	86,74
*****	*******	70	168	68 F	18/10/2019	2,02	2,75	73,00	85,22	82,85
*****	*******	71	167	67 F	17/06/2021	2,22	3,29	67,58	96,34	109,85
*****	*******	71	167	67 F	15/07/2021	2,20	3,08	71,56	95,46	102,80
*****	*******	72	167	67 F	11/11/2021	1,99	2,97	66,84	87,24	100,41
*****	*******	72	167	67 F	13/01/2022	2,10	3,00	70,12	92,34	101,32
*****	*******	72	167	67 F	07/04/2022	1,85	2,55	72,46	81,14	86,16
*****	*******	72	167	67 F	30/06/2022	2,24	3,73	60,00	98,18	125,89
*****	*******	72	167	67 F	22/09/2022	2,02	3,21	63,02	88,85	108,47
*****	*******	73	167	67 F	12/01/2023	2,10	3,14	66,89	93,39	107,18
*****	*******	73	167	67 F	26/01/2023	2,12	3,00	70,73	94,34	102,39
*****	*******	73	167	67 F	09/02/2023	2,04	3,04	67,31	90,96	103,74
*****	*******	73	167	67 F	09/03/2023	1,62	2,55	63,54	72,15	87,18
*****	*******	73	167	67 F	23/03/2023	1,77	2,57	68,83	78,74	87,82
*****	*******	73	167	67 F	21/04/2023	2,19	3,44	63,55	97,34	117,58
*****	*******	73	167	67 F	18/05/2023	1,98	2,89	68,34	87,97	98,82
*****	*******	73	167	67 F	22/06/2023	2,00	3,15	63,61	89,14	107,59
*****	*******	73	167	67 F	14/09/2023	1,89	3,00	62,87	83,89	102,44
*****	*******	74	167	67 F	14/12/2023	2,21	3,23	68,59	99,81	111,48
*****	*******	80	154	68 F	02/11/2015	0,00	0,00		0,00	0,00
*****	*******	81	154	68 F	18/11/2015	1,09	1,88	57,00	67,06	76,23
*****	*******	81	154	68 F	11/02/2016	0,94	1,65	56,00	57,60	66,88
*****	*******	81	154	66 F	04/05/2016	0,91	1,45	62,00	56,03	59,05
*****	*******	81	154	66 F	28/07/2016	1,02	1,42	71,00	62,78	57,80
*****	*******	81	154	68 F	26/10/2016	0,96	1,46	65,00	58,62	59,29
*****	*******	82	154	69 F	17/01/2017	1,08	1,52	71,00	67,41	62,47
*****	*******	82	154	67 F	27/06/2017	1,07	1,51	70,00	66,84	61,88
*****	*******	82	154	60 F	14/09/2017	2,12	2,76	76,85	126,15	125,23
*****	*******	82	154	66 F	21/09/2017	1,11	1,56	71,00	67,14	64,61
*****	*******	83	154	66 F	21/12/2017	0,97	1,54	62,00	58,16	63,83
*****	*******	83	154	66 F	19/03/2018	1,07	1,58	67,00	64,86	65,48
*****	*******	83	154	62 F	14/06/2018	1,21	1,69	71,00	73,32	70,49
*****	*******	83	154	62 F	06/09/2018	0,99	1,46	67,00	60,54	60,80
*****	*******	84	154	62 F	05/12/2018	1,08	1,62	66,00	65,62	67,89
*****	*******	84	154	62 F	07/03/2019	1,09	1,53	71,00	66,97	64,04
*****	*******	84	154	62 F	06/06/2019	1,16	1,58	73,00	71,83	66,43
*****	*******	84	154	62 F	05/09/2019	1,11	1,58	70,00	68,71	66,34
*****	*******	64	154	64 F	14/09/2015	2,39	2,85	83,00	116,61	100,91
*****	*******	64	154	64 F	14/12/2015	2,53	2,91	86,00	123,45	103,36
*****	*******	64	154	66 F	07/03/2016	2,47	2,88	85,00	120,63	102,07
*****	*******	64	154	66 F	25/05/2016	2,42	2,92	82,00	118,13	103,37
*****	*******	65	154	66 F	29/08/2016	2,21	2,58	85,00	108,64	92,23
*****	*******	65	154	65 F	23/11/2016	2,35	2,71	86,00	115,72	96,77
*****	*******	65	154	66 F	20/02/2017	2,30	2,68	85,00	113,37	95,73
*****	*******	65	154	66 F	22/05/2017	2,36	2,71	87,00	116,36	96,75
*****	*******	66	154	66 F	02/11/2017	2,39	2,76	86,00	115,36	99,69
*****	*******	66	154	66 F	15/02/2018	2,18	2,57	84,00	105,73	93,29
*****	*******	67	154	66 F	20/09/2018	2,18	2,59	84,00	106,43	94,04
*****	*******	67	154	68 F	28/02/2019	2,17	2,55	85,00	106,66	92,99
*****	*******	67	154	68 F	23/05/2019	2,21	2,68	82,00	109,04	97,71
*****	*******	67	154	69 F	08/08/2019	2,23	2,52	88,00	110,60	92,24
*****	*******	69	153	67 F	17/09/2020	2,26	2,85	79,27	114,70	113,36

*****	*******	69	153	67	F	10/12/2020	2,22	2,70	82,28	112,79	107,40
*****	*******	69	153	67	F	11/03/2021	2,24	2,78	80,43	113,70	110,75
*****	*******	69	153	67	F	03/06/2021	2,22	2,76	80,44	112,67	109,72
*****	*******	70	153	67	F	26/08/2021	2,21	2,74	80,67	113,94	110,48
*****	*******	70	153	67	F	18/11/2021	2,12	2,64	80,26	109,24	106,47
*****	*******	70	153	67	F	10/02/2022	2,09	2,62	79,60	107,50	105,64
*****	*******	70	153	67	F	04/08/2022	2,10	2,58	81,50	108,19	103,84
*****	*******	71	153	67	F	27/10/2022	2,12	2,74	77,37	110,74	111,72
*****	*******	91	166	66	M	25/09/2015	1,12	2,52	44,00	44,25	65,33
*****	*******	91	166	66	M	18/12/2015	1,06	2,73	38,00	42,05	70,60
*****	*******	91	166	66	M	19/03/2016	0,99	2,52	39,00	39,17	65,23
*****	*******	92	166	62	M	14/10/2016	0,97	2,37	40,00	38,49	61,68
*****	*******	92	166	60	M	20/01/2017	0,98	2,47	39,00	39,22	64,16
*****	*******	93	166	62	M	21/04/2017	1,08	2,52	42,00	43,39	65,90
*****	*******	93	166	61	M	21/07/2017	0,94	2,23	42,00	37,74	58,32
*****	*******	93	166	61	M	26/10/2017	0,88	2,48	35,00	35,64	64,98
*****	*******	93	166	61	M	25/01/2018	0,77	2,35	32,00	31,18	61,52
*****	*******	94	166	60	M	19/04/2018	0,98	2,46	39,00	39,80	64,52
*****	*******	94	166	60	M	12/07/2018	1,00	2,44	40,00	40,57	64,16
*****	*******	94	166	60	M	04/10/2018	0,84	2,31	36,00	34,37	60,58
*****	*******	94	166	60	M	10/01/2019	0,70	2,03	34,00	28,71	53,25
*****	*******	95	166	60	M	04/04/2019	0,95	2,48	38,00	38,88	65,13
*****	*******	95	166	59	M	04/07/2019	0,92	2,28	40,00	37,54	60,09
*****	*******	95	166	59	M	10/10/2019	0,95	2,20	43,00	39,01	57,99
*****	*******	63	145	72	F	20/10/2015	1,76	2,44	72,00	98,19	100,36
*****	*******	63	145	73	F	14/01/2016	1,30	1,95	66,00	72,73	80,19
*****	*******	64	145	72	F	22/04/2016	1,26	1,85	68,00	71,12	76,71
*****	*******	64	145	71	F	28/07/2016	1,45	2,07	70,00	81,89	85,71
*****	*******	64	145	74	F	26/10/2016	1,39	1,94	71,00	78,68	80,35
*****	*******	64	145	72	F	19/01/2017	1,54	2,08	74,00	87,25	86,33
*****	*******	65	145	71	F	04/04/2017	1,50	2,09	71,00	86,15	87,58
*****	*******	65	145	70	F	27/06/2017	1,26	1,86	67,00	72,56	77,89
*****	*******	65	145	71	F	26/09/2017	1,49	2,10	70,00	81,31	88,81
*****	*******	65	145	71	F	21/12/2017	1,53	2,09	73,00	83,47	88,25
*****	*******	66	145	71	F	15/03/2018	1,73	2,16	80,00	95,31	91,53
*****	*******	66	145	67	F	07/06/2018	1,79	2,33	76,00	98,30	98,59
*****	*******	66	145	69	F	04/10/2018	1,72	2,34	73,00	95,13	99,46
*****	*******	67	145	68	F	07/02/2019	1,73	2,24	77,00	96,20	95,72
*****	*******	67	145	68	F	04/04/2019	1,76	2,37	74,00	97,85	101,43
*****	*******	67	145	69	F	04/07/2019	1,51	2,16	69,00	84,37	92,25
*****	*******	67	145	69	F	17/10/2019	1,42	2,02	70,00	79,25	86,54
*****	*******	23	159	69	F	01/10/2015	2,56	2,95	86,00	79,16	75,46
*****	*******	23	159	74	F	22/12/2015	2,48	2,93	84,00	76,53	74,90
*****	*******	23	159	74	F	08/03/2016	2,72	3,24	83,00	83,86	82,89
*****	*******	24	159	81	F	24/05/2016	2,73	3,26	83,00	85,17	83,71
*****	*******	24	159	82	F	24/08/2016	2,54	2,94	86,00	79,07	75,46
*****	*******	24	159	82	F	02/12/2016	2,50	2,92	85,00	78,00	75,06
*****	*******	24	159	84	F	02/03/2017	2,64	3,12	84,00	82,10	80,19
*****	*******	25	159	83	F	01/06/2017	2,55	3,05	83,00	79,86	78,83
*****	*******	25	159	83	F	29/09/2017	2,27	2,76	82,00	72,70	71,59
*****	*******	25	161	82	F	12/12/2017	3,13	3,91	79,87	97,24	104,91
*****	*******	25	159	82	F	14/12/2017	2,61	3,12	83,00	83,59	81,03
*****	*******	25	159	82	F	11/01/2018	2,39	2,83	84,00	76,75	73,48
*****	*******	25	161	82	F	23/01/2018	2,47	3,56	69,36	76,87	95,50
*****	*******	25	161	82	F	23/01/2018	2,54	2,95	85,95	78,95	79,15
*****	*******	25	161	82	F	29/01/2018	2,75	3,65	75,27	85,56	97,95
*****	*******	26	159	84	F	26/04/2018	2,46	2,90	84,00	78,85	75,52
*****	*******	26	159	82	F	19/07/2018	2,49	3,00	83,00	79,97	78,05
*****	*******	26	159	82	F	11/10/2018	2,57	2,99	85,00	82,71	78,00
*****	*******	27	159	77	F	02/05/2019	2,45	2,90	84,00	79,14	75,86
*****	*******	27	159	76	F	31/07/2019	2,59	3,01	86,00	83,57	78,85
*****	*******	27	159	74	F	31/10/2019	2,45	2,94	83,00	79,14	77,14
*****	*******	28	161	82	F	15/10/2020	2,42	3,05	79,18	76,10	81,93
*****	*******	28	161	82	F	14/01/2021	2,50	3,09	81,09	78,86	82,92
*****	*******	29	161	82	F	08/07/2021	2,50	3,12	80,30	79,20	83,80
*****	*******	29	161	82	F	30/12/2021	2,43	3,07	79,11	76,71	82,39
*****	*******	29	161	82	F	24/03/2022	2,38	2,96	80,56	75,34	79,48
*****	*******	30	161	82	F	23/06/2022	2,40	2,89	83,19	76,28	77,66
*****	*******	30	161	82	F	15/09/2022	2,23	2,78	80,39	70,92	74,72
*****	*******	30	161	82	F	15/12/2022	2,22	2,74	81,02	70,64	73,84

*****	*******	31	161	82	F	24/08/2023	2,15	2,69	79,95	68,60	72,44
*****	*******	31	161	82	F	09/11/2023	2,10	2,65	79,18	66,92	71,36
*****	*******	23	161	52	M	13/03/2017	3,22	3,97	81,00	86,83	87,80
*****	*******	41	157	92	F	06/11/2015	2,20	2,86	76,00	81,23	83,61
*****	*******	42	157	90	F	26/04/2016	1,88	2,34	80,00	69,99	69,10
*****	*******	42	157	90	F	10/08/2016	1,89	2,51	75,00	70,64	74,15
*****	*******	43	157	90	F	06/04/2017	1,94	2,53	76,00	72,80	75,19
*****	*******	43	157	91	F	11/07/2017	1,82	2,34	77,00	67,16	69,32
*****	*******	43	157	91	F	09/10/2017	1,65	2,13	77,00	60,93	63,24
*****	*******	43	157	90	F	04/01/2018	1,75	2,23	78,00	64,86	66,48
*****	*******	44	157	94	F	26/04/2018	1,34	1,80	74,00	49,77	53,62
*****	*******	44	157	94	F	26/07/2018	1,51	1,92	78,00	56,31	57,45
*****	*******	44	157	92	F	18/10/2018	1,87	2,45	76,00	69,59	73,45
*****	*******	44	157	90	F	24/01/2019	1,65	2,31	71,00	61,62	69,42
*****	*******	45	157	90	F	26/04/2019	1,34	1,87	71,00	50,13	56,15
*****	*******	45	157	90	F	25/07/2019	1,53	2,12	72,00	57,41	63,79
*****	*******	45	157	85	F	03/10/2019	1,37	1,95	70,00	51,59	58,87
*****	*******	46	153	86	F	19/11/2020	1,49	2,43	61,35	59,16	78,47
*****	*******	46	153	86	F	18/03/2021	1,11	1,27	87,87	44,11	40,85
*****	*******	47	153	86	F	15/04/2021	1,23	1,31	94,05	49,37	42,64
*****	*******	47	153	86	F	08/07/2021	1,73	2,17	79,77	69,34	70,60
*****	*******	47	153	86	F	07/10/2021	1,04	1,25	83,63	41,70	40,50
*****	*******	47	153	86	F	04/11/2021	1,46	2,01	72,42	58,27	65,35
*****	*******	47	153	86	F	02/12/2021	0,78	1,23	63,03	31,06	40,03
*****	*******	48	153	86	F	31/03/2022	1,39	2,11	65,93	56,06	68,94
*****	*******	48	153	86	F	30/06/2022	1,31	1,99	65,53	52,71	65,22
*****	*******	48	153	86	F	22/09/2022	1,66	2,28	73,09	67,18	74,53
*****	*******	50	162	115	F	18/09/2015	0,82	2,41	34,00	30,71	69,57
*****	*******	51	162	115	F	09/12/2015	1,11	2,93	37,00	42,38	84,95
*****	*******	54	162	88	F	27/03/2019	1,69	3,09	54,00	64,28	91,30
*****	*******	20	180	68	M	04/07/2017	4,72	5,36	88,00	99,99	91,39
*****	*******	20	180	67	M	05/09/2017	4,80	5,05	95,00	102,00	86,46
*****	*******	20	180	65	M	14/12/2017	4,66	4,99	93,00	99,18	85,47
*****	*******	21	180	68	M	08/03/2018	4,71	5,15	91,00	100,26	88,11
*****	*******	21	180	68	M	07/06/2018	4,54	4,96	91,00	96,71	85,11
*****	*******	46	157	83	F	18/09/2015	2,18	2,87	75,00	84,43	86,85
*****	*******	47	157	93	F	02/03/2016	1,79	2,67	67,00	69,74	81,23
*****	*******	47	157	93	F	19/03/2016	1,52	2,27	66,00	59,44	68,85
*****	*******	47	157	93	F	29/03/2016	1,57	2,52	62,00	61,46	76,66
*****	*******	47	157	97	F	28/04/2016	1,04	1,67	62,00	40,78	50,89
*****	*******	47	157	98	F	28/07/2016	1,59	2,44	65,00	62,15	74,27
*****	*******	47	157	99	F	19/09/2016	1,41	1,92	73,00	54,89	58,45
*****	*******	47	157	99	F	27/10/2016	1,64	2,43	67,00	64,04	73,91
*****	*******	48	157	99	F	24/01/2017	1,58	1,72	91,00	62,63	52,69
*****	*******	48	157	97	F	19/04/2017	2,11	2,90	72,00	83,55	88,66
*****	*******	48	157	94	F	20/07/2017	1,90	2,41	78,00	73,33	73,82
*****	*******	48	157	94	F	18/10/2017	2,01	2,46	81,00	77,82	75,67
*****	*******	49	157	92	F	10/01/2018	1,77	2,35	75,00	68,69	72,49
*****	*******	49	157	95	F	11/04/2018	2,20	2,85	77,00	85,75	88,03
*****	*******	49	157	97	F	10/07/2018	1,92	2,45	78,00	75,07	75,95
*****	*******	49	157	95	F	05/11/2018	1,69	2,13	79,00	66,17	65,82
*****	*******	50	157	95	F	13/02/2019	1,48	1,70	87,00	57,93	52,68
*****	*******	50	157	98	F	07/05/2019	1,71	2,23	76,00	67,38	69,26
*****	*******	50	157	97	F	28/08/2019	2,03	2,51	80,00	79,76	78,35
*****	*******	53	156	96	F	20/01/2022	1,55	2,18	71,02	62,85	70,95
*****	*******	53	156	96	F	07/04/2022	1,54	1,82	84,43	62,37	59,23
*****	*******	53	156	96	F	07/07/2022	1,30	2,05	63,36	52,83	66,86
*****	*******	54	156	96	F	18/08/2023	2,16	2,95	73,28	88,53	96,67
*****	*******	54	156	96	F	10/11/2023	1,65	2,09	79,07	67,61	68,42
*****	*******	46	174	64	M	08/01/2016	2,17	3,77	57,00	56,03	74,39
*****	*******	47	175	63	M	11/03/2016	2,47	4,46	55,30	63,59	91,39
*****	*******	47	175	63	M	31/03/2016	3,50	4,52	77,38	90,13	92,55
*****	*******	47	174	64	M	25/04/2016	2,35	3,79	62,00	60,97	74,96
*****	*******	47	174	60	M	13/07/2016	2,72	4,35	62,00	70,66	86,19
*****	*******	47	174	60	M	09/08/2016	2,49	3,93	63,00	64,59	77,75
*****	*******	47	174	59	M	09/09/2016	2,43	4,04	60,00	63,01	79,97
*****	*******	47	174	60	M	06/10/2016	2,32	3,86	60,00	60,39	76,39
*****	*******	47	174	61	M	08/11/2016	2,84	4,11	69,00	73,69	81,37
*****	*******	47	174	60	M	02/12/2016	2,59	4,26	60,00	67,25	84,28
*****	*******	47	174	63	M	27/02/2017	2,57	4,01	64,00	66,74	79,45

*****	*******	48	174	62	M	31/05/2017	2,39	3,89	61,00	62,34	77,13
*****	*******	48	174	62	M	21/09/2017	2,65	4,08	64,00	69,50	81,08
*****	*******	48	174	63	M	21/12/2017	2,63	3,84	68,00	68,85	76,26
*****	*******	49	174	63	M	28/03/2018	2,68	3,99	67,00	70,29	79,44
*****	*******	49	174	61	M	26/06/2018	2,64	3,85	68,00	69,23	76,66
*****	*******	49	174	60	M	20/09/2018	2,71	3,90	69,00	71,34	77,75
*****	*******	49	174	60	M	20/12/2018	2,50	3,80	65,00	65,74	75,85
*****	*******	50	174	60	M	28/03/2019	2,62	3,91	67,00	69,25	78,11
*****	*******	50	174	59	M	27/06/2019	2,57	3,87	66,00	67,94	77,49
*****	*******	50	174	58	M	03/10/2019	2,63	3,76	69,00	69,58	75,17
*****	*******	51	175	63	M	24/09/2020	2,70	4,01	67,32	71,75	84,08
*****	*******	51	175	63	M	22/12/2020	2,69	3,98	67,78	71,57	83,30
*****	*******	52	175	63	M	18/03/2021	2,54	3,74	67,83	67,97	78,95
*****	*******	52	175	63	M	17/06/2021	2,44	3,73	65,26	65,21	78,72
*****	*******	52	175	63	M	23/09/2021	2,40	3,61	66,52	64,30	76,16
*****	*******	52	175	63	M	23/12/2021	2,47	3,99	61,93	66,11	84,10
*****	*******	53	175	63	M	17/03/2022	2,43	3,86	62,97	65,58	81,88
*****	*******	53	175	63	M	16/06/2022	2,41	3,92	61,35	64,95	83,24
*****	*******	53	175	63	M	22/09/2022	2,27	3,62	62,76	61,33	76,82
*****	*******	53	175	63	M	09/03/2023	2,34	3,77	62,20	63,28	79,98
*****	*******	54	175	63	M	15/06/2023	2,39	3,54	67,42	65,09	75,76
*****	*******	54	175	63	M	13/07/2023	2,51	3,51	71,52	68,44	75,09
*****	*******	54	175	63	M	07/09/2023	2,22	3,63	61,12	60,43	77,59
*****	*******	54	175	63	M	05/10/2023	2,57	3,78	67,95	70,02	80,87
*****	*******	75	158	72	F	04/11/2015	1,48	2,15	68,00	78,56	78,31
*****	*******	75	158	75	F	12/02/2016	0,98	1,53	64,00	51,98	55,84
*****	*******	76	158	75	F	08/04/2016	0,97	1,53	63,00	52,36	56,18
*****	*******	76	158	75	F	01/07/2016	1,25	1,82	68,00	67,29	66,90
*****	*******	76	158	75	F	23/09/2016	0,92	1,35	68,00	49,30	49,58
*****	*******	76	158	74	F	20/12/2016	1,14	1,72	66,00	61,18	63,20
*****	*******	77	158	77	F	17/03/2017	1,30	1,77	73,00	70,89	65,68
*****	*******	77	158	76	F	16/06/2017	1,29	1,86	69,00	70,23	69,06
*****	*******	77	158	76	F	14/09/2017	1,69	2,27	74,00	90,12	84,33
*****	*******	77	158	76	F	01/03/2018	1,51	2,12	71,00	81,07	79,09
*****	*******	78	158	71	F	26/07/2018	1,33	1,93	68,00	71,78	72,42
*****	*******	78	158	68	F	25/10/2018	0,98	1,55	63,00	53,44	58,16
*****	*******	78	158	67	F	17/01/2019	1,39	2,04	68,00	75,70	76,62
*****	*******	79	158	68	F	11/07/2019	0,93	1,59	58,00	51,23	59,99
*****	*******	81	155	73	F	25/03/2021	1,03	1,52	67,80	59,59	67,11
*****	*******	21	166	61	M	05/11/2020	4,10	5,63	72,82	102,29	120,41
*****	*******	21	166	61	M	28/01/2021	4,42	5,72	77,24	110,28	122,37
*****	*******	21	166	61	M	22/04/2021	4,24	5,34	79,32	105,70	114,23
*****	*******	22	166	61	M	15/07/2021	4,10	5,46	75,21	102,30	116,23
*****	*******	22	166	61	M	14/10/2021	4,22	5,59	75,50	105,31	119,19
*****	*******	22	166	61	M	13/01/2022	4,19	5,70	73,52	104,41	121,36
*****	*******	22	166	61	M	21/04/2022	4,30	5,75	74,89	107,33	122,47
*****	*******	23	166	61	M	14/07/2022	4,08	5,48	74,49	101,86	116,54
*****	*******	23	166	61	M	20/10/2022	4,10	5,73	71,56	102,34	121,90
*****	*******	23	166	61	M	19/01/2023	4,09	5,55	73,77	102,24	118,13
*****	*******	23	166	61	M	13/04/2023	3,98	5,72	69,55	99,36	121,76
*****	*******	24	166	61	M	06/07/2023	4,16	5,93	70,21	104,27	126,19
*****	*******	24	166	61	M	28/09/2023	4,05	5,61	72,10	101,37	119,46
*****	*******	24	166	61	M	21/12/2023	3,95	5,70	69,32	98,95	121,28
*****	*******	20	177	60	F	10/12/2020	2,66	3,45	77,00	66,62	75,04
*****	*******	20	177	60	F	11/03/2021	2,63	3,40	77,43	65,97	73,89
*****	*******	20	177	60	F	03/06/2021	2,60	3,56	73,12	65,29	77,45
*****	*******	21	177	60	F	26/08/2021	2,53	3,30	76,56	63,47	71,61
*****	*******	21	177	60	F	18/11/2021	2,66	3,66	72,70	66,85	79,44
*****	*******	21	177	60	F	10/02/2022	2,64	3,31	79,63	66,15	71,76
*****	*******	21	177	60	F	05/05/2022	2,79	3,61	77,22	70,03	78,35
*****	*******	22	177	60	F	14/07/2022	2,56	3,23	79,32	64,43	69,88
*****	*******	22	177	60	F	06/10/2022	2,64	3,33	79,15	66,31	72,09
*****	*******	22	177	60	F	02/02/2023	2,72	3,35	81,12	68,36	72,51
*****	*******	22	177	60	F	27/04/2023	2,60	3,17	82,06	65,40	68,57
*****	*******	23	177	60	F	26/10/2023	2,51	2,94	85,45	63,43	63,61
*****	*******	23	177	60	F	18/01/2024	2,69	3,29	81,79	67,95	71,19
*****	*******	21	175	88	F	07/07/2022	4,10	4,52	90,79	105,55	100,58
*****	*******	60	169	58	M	18/01/2024	2,25	3,41	65,84	70,06	83,04
*****	*******	38	163	65	F	23/11/2015	3,54	4,27	82,00	118,53	113,35
*****	*******	38	163	65	F	11/01/2016	3,34	4,02	83,00	111,73	106,66

*****	*******	38	163	65	F	18/03/2016	2,86	3,37	84,00	95,81	89,51
*****	*******	38	162	70	F	05/05/2016	5,01	5,02	99,94	164,82	136,03
*****	*******	38	162	70	F	24/05/2016	4,11	4,86	84,61	135,11	131,71
*****	*******	38	163	65	F	01/08/2016	3,33	4,12	80,00	111,43	109,20
*****	*******	39	163	67	F	28/09/2016	3,54	4,25	83,00	119,52	113,25
*****	*******	39	163	64	F	06/02/2017	2,48	2,96	83,00	83,67	78,92
*****	*******	39	163	64	F	08/02/2017	2,94	3,48	84,00	99,43	92,70
*****	*******	39	163	64	F	10/02/2017	3,34	4,04	82,00	112,71	107,64
*****	*******	39	163	64	F	13/02/2017	3,45	4,10	84,00	116,46	109,44
*****	*******	39	163	64	F	15/02/2017	3,13	3,73	83,00	105,64	99,51
*****	*******	39	163	64	F	24/02/2017	3,57	4,24	84,00	120,46	112,99
*****	*******	39	163	66	F	06/03/2017	3,55	4,35	81,00	120,08	116,07
*****	*******	39	163	66	F	22/03/2017	3,48	4,10	84,00	117,62	109,25
*****	*******	39	163	67	F	03/04/2017	3,50	4,24	82,00	118,37	113,09
*****	*******	39	163	67	F	02/05/2017	3,59	4,27	84,00	121,12	113,90
*****	*******	39	163	65	F	29/05/2017	3,69	4,45	82,00	124,65	118,62
*****	*******	39	163	65	F	28/08/2017	3,61	4,34	83,00	119,04	116,23
*****	*******	40	163	65	F	28/09/2017	3,56	4,26	83,00	117,45	114,21
*****	*******	40	163	65	F	06/10/2017	2,94	3,61	81,00	97,14	96,69
*****	*******	40	163	65	F	10/10/2017	3,05	3,63	84,00	100,70	97,34
*****	*******	40	163	65	F	13/10/2017	2,96	3,57	82,00	97,67	95,64
*****	*******	40	163	65	F	16/10/2017	3,08	3,75	82,00	101,73	100,43
*****	*******	40	163	65	F	23/10/2017	3,27	4,07	80,00	107,76	109,09
*****	*******	40	163	66	F	27/11/2017	3,53	4,20	84,00	116,56	112,48
*****	*******	40	163	66	F	11/12/2017	3,08	3,90	78,00	101,61	104,67
*****	*******	40	163	66	F	15/12/2017	3,13	3,86	81,00	103,32	103,64
*****	*******	40	163	66	F	18/12/2017	3,27	4,03	81,00	107,89	108,23
*****	*******	40	163	66	F	21/12/2017	3,54	4,36	81,00	117,00	117,08
*****	*******	40	163	66	F	21/02/2018	3,24	4,00	81,00	107,37	107,65
*****	*******	40	163	68	F	26/02/2018	3,42	4,16	82,00	113,40	111,76
*****	*******	40	163	68	F	21/05/2018	3,54	4,22	83,00	117,22	113,46
*****	*******	41	163	68	F	24/09/2018	3,68	4,35	84,00	122,32	117,29
*****	*******	41	163	68	F	01/10/2018	3,42	4,21	81,00	113,54	113,41
*****	*******	41	163	68	F	10/12/2018	3,54	4,22	83,00	118,10	113,96
*****	*******	41	163	70	F	04/03/2019	3,58	4,26	84,00	119,31	115,21
*****	*******	41	163	70	F	29/03/2019	3,38	4,10	82,00	112,81	110,94
*****	*******	41	163	70	F	10/04/2019	3,49	4,13	84,00	116,47	111,74
*****	*******	41	163	69	F	27/05/2019	3,62	4,36	83,00	121,22	118,18
*****	*******	42	163	69	F	19/09/2019	3,49	4,14	84,00	117,08	112,07
*****	*******	43	162	70	F	24/09/2020	3,65	4,39	83,26	124,97	122,03
*****	*******	43	162	70	F	17/12/2020	3,64	4,36	83,41	124,58	121,43
*****	*******	43	162	70	F	11/03/2021	3,46	4,18	82,67	118,38	116,43
*****	*******	43	162	70	F	03/06/2021	3,59	4,24	84,78	122,99	117,95
*****	*******	44	162	70	F	16/12/2021	3,53	4,26	82,79	121,92	119,40
*****	*******	44	162	70	F	10/03/2022	3,82	4,61	82,91	131,95	129,03
*****	*******	44	162	70	F	28/07/2022	3,58	4,37	81,90	123,56	122,31
*****	*******	45	162	70	F	20/10/2022	3,50	4,33	80,77	121,88	122,06
*****	*******	45	162	70	F	12/01/2023	3,49	4,21	82,78	121,47	118,71
*****	*******	45	162	70	F	30/03/2023	3,52	4,19	83,90	122,51	118,13
*****	*******	45	162	70	F	22/06/2023	3,50	4,24	82,39	121,79	119,59
*****	*******	46	162	70	F	07/12/2023	3,59	4,31	83,39	126,21	122,16
*****	*******	31	156	64	F	16/11/2017	0,80	1,93	41,00	27,26	53,86
*****	*******	31	155	61	F	19/02/2018	0,74	2,08	35,00	25,78	58,73
*****	*******	31	155	60	F	21/03/2018	1,77	3,16	56,00	61,51	89,34
*****	*******	31	155	60	F	20/04/2018	1,80	3,21	56,00	62,62	90,65
*****	*******	32	155	60	F	16/05/2018	1,53	3,11	49,00	53,17	87,98
*****	*******	32	155	61	F	14/06/2018	1,66	3,08	53,00	57,89	87,36
*****	*******	32	155	62	F	12/07/2018	1,58	3,02	52,00	54,99	85,62
*****	*******	32	155	66	F	10/10/2018	1,57	3,16	49,00	54,57	89,61
*****	*******	32	155	67	F	05/02/2019	1,75	3,10	56,00	61,08	88,01
*****	*******	33	155	70	F	07/05/2019	1,78	3,14	56,00	62,11	89,17
*****	*******	33	155	72	F	21/08/2019	1,40	3,02	46,00	48,99	86,13
*****	*******	46	155	80	F	25/02/2016	0,67	2,28	29,00	26,65	70,52
*****	*******	46	155	79	F	11/03/2016	0,99	2,95	33,00	38,96	91,09
*****	*******	46	155	79	F	23/03/2016	1,08	3,33	32,00	42,67	102,77
*****	*******	46	155	79	F	08/04/2016	0,91	2,65	34,00	35,96	81,79
*****	*******	46	155	79	F	22/04/2016	1,31	3,08	42,00	51,73	95,19
*****	*******	46	155	80	F	15/07/2016	1,07	2,77	38,00	42,46	85,42
*****	*******	47	155	78	F	07/10/2016	1,14	3,44	33,00	45,35	106,78
*****	*******	47	155	73	F	24/03/2017	1,05	3,10	33,00	41,82	96,38

*****	*******	48	155	73	F	13/10/2017	0,93	2,62	35,00	36,42	81,97
*****	*******	48	155	74	F	13/11/2017	1,01	2,76	36,00	39,65	86,29
*****	*******	48	155	73	F	12/01/2018	1,15	3,03	37,00	45,21	94,90
*****	*******	48	155	71	F	06/04/2018	1,13	3,12	36,00	44,64	97,88
*****	*******	48	155	69	F	29/06/2018	1,29	3,10	41,00	51,14	97,44
*****	*******	49	155	67	F	14/09/2018	0,82	2,82	29,00	32,41	88,76
*****	*******	49	155	72	F	21/12/2018	1,02	2,85	35,00	40,33	89,99
*****	*******	49	155	69	F	12/04/2019	1,01	3,06	33,00	40,27	96,45
*****	*******	49	155	70	F	19/07/2019	1,11	3,18	34,00	44,32	100,72
*****	*******	52	157	85	F	01/09/2022	0,71	2,60	27,17	28,03	82,78
*****	*******	53	157	85	F	22/12/2022	0,73	2,19	33,41	29,26	70,13
*****	*******	53	157	85	F	04/01/2023	1,11	3,01	36,95	44,51	96,47
*****	*******	53	157	85	F	19/01/2023	0,81	2,76	29,38	32,49	88,55
*****	*******	53	157	85	F	16/02/2023	0,83	2,59	31,85	33,10	83,22
*****	*******	53	157	85	F	02/03/2023	0,79	2,48	31,93	31,76	79,67
*****	*******	53	157	85	F	16/03/2023	0,73	2,38	30,90	29,42	76,25
*****	*******	53	157	85	F	20/04/2023	0,70	2,57	27,32	28,11	82,42
*****	*******	53	157	85	F	04/05/2023	0,89	2,99	29,90	35,77	95,81
*****	*******	53	157	85	F	13/07/2023	0,74	1,76	42,32	29,81	56,42
*****	*******	53	157	85	F	24/08/2023	0,76	1,79	42,42	30,40	57,39
*****	*******	54	157	85	F	09/11/2023	0,82	2,32	35,27	33,05	74,96
*****	*******	54	157	85	F	07/12/2023	0,81	2,87	28,25	32,80	92,85
*****	*******	54	157	85	F	01/02/2024	0,95	2,93	32,48	38,47	94,73
*****	*******	42	161	79	F	15/06/2018	1,27	2,01	63,00	43,69	55,86
*****	*******	42	161	86	F	14/01/2019	1,10	1,80	61,00	38,20	50,33
*****	*******	43	161	83	F	31/07/2019	1,50	2,29	65,00	52,18	64,19
*****	*******	43	161	82	F	27/08/2019	1,02	1,69	60,00	35,41	47,28
*****	*******	43	161	83	F	23/09/2019	1,22	1,95	62,00	42,63	54,55
*****	*******	45	162	82	F	09/09/2021	1,26	2,07	61,12	51,09	68,10
*****	*******	45	162	82	F	02/12/2021	1,47	2,43	60,64	59,50	79,94
*****	*******	45	162	82	F	24/02/2022	1,36	2,34	58,22	54,94	76,88
*****	*******	46	162	82	F	19/05/2022	1,39	2,32	59,98	56,67	76,83
*****	*******	46	162	82	F	17/11/2022	1,39	2,41	57,87	56,74	79,72
*****	*******	46	162	82	F	19/01/2023	1,17	2,11	55,53	47,85	70,07
*****	*******	47	162	82	F	13/04/2023	1,25	2,16	57,97	51,45	72,02
*****	*******	47	162	82	F	06/07/2023	1,40	2,23	62,87	57,69	74,47
*****	*******	38	154	53	F	24/07/2019	2,17	3,41	63,00	79,33	101,51
*****	*******	38	154	55	F	27/08/2019	2,10	3,34	62,00	77,10	99,40
*****	*******	38	154	57	F	26/09/2019	1,81	3,17	57,00	66,21	94,46
*****	*******	40	154	50	F	20/01/2022	1,81	3,13	57,93	67,46	96,16
*****	*******	40	154	50	F	21/04/2022	1,94	3,36	57,80	72,22	103,16
*****	*******	41	154	50	F	14/07/2022	1,79	3,22	55,60	67,14	99,41
*****	*******	41	154	50	F	26/01/2023	2,30	3,42	67,15	86,10	105,56
*****	*******	42	154	50	F	29/12/2023	1,59	3,03	52,36	59,98	94,04
*****	*******	33	158	50	F	29/12/2015	1,56	2,86	54,00	52,88	78,33
*****	*******	34	158	50	F	25/02/2016	1,71	3,16	54,00	58,32	86,99
*****	*******	34	158	51	F	23/03/2016	1,73	3,02	57,00	59,21	83,17
*****	*******	34	158	51	F	20/04/2016	1,52	2,82	53,00	51,87	77,74
*****	*******	34	158	53	F	28/07/2016	1,80	3,21	56,00	61,54	88,47
*****	*******	34	158	54	F	19/10/2016	1,76	3,07	57,00	60,02	84,59
*****	*******	34	158	54	F	20/01/2017	1,78	3,23	55,00	60,80	88,91
*****	*******	35	155	52	F	26/04/2017	1,83	4,08	44,00	65,26	117,53
*****	*******	35	155	48	F	29/06/2017	1,88	3,29	57,00	66,77	94,92
*****	*******	35	155	47	F	26/09/2017	1,86	3,25	57,00	65,80	93,97
*****	*******	35	155	49	F	28/12/2017	1,74	3,13	55,00	61,84	90,84
*****	*******	36	155	50	F	25/04/2018	1,85	3,09	59,00	66,09	89,57
*****	*******	36	155	49	F	26/07/2018	1,85	3,11	59,00	66,00	90,40
*****	*******	36	155	48	F	25/10/2018	1,84	3,10	59,00	65,61	90,05
*****	*******	37	155	49	F	31/01/2019	1,81	3,19	56,00	64,92	92,94
*****	*******	37	155	52	F	19/07/2019	1,83	3,12	58,00	65,72	91,29
*****	*******	19	167	57	M	11/01/2016	3,53	4,35	81,00	86,11	87,18
*****	*******	19	167	57	M	07/04/2016	3,42	4,25	80,00	83,42	85,22
*****	*******	19	167	53	M	27/06/2016	3,47	4,10	84,00	84,62	82,21
*****	*******	19	167	56	M	06/10/2016	3,32	4,12	80,00	80,91	82,52
*****	*******	20	167	56	M	27/03/2017	3,04	4,15	73,00	74,66	83,57
*****	*******	20	167	56	M	20/06/2017	2,36	3,94	59,00	58,05	79,29
*****	*******	20	167	57	M	11/10/2017	2,57	4,15	61,00	63,23	83,58
*****	*******	21	167	58	M	10/01/2018	3,10	4,21	73,00	76,50	84,81
*****	*******	21	167	58	M	13/04/2018	3,27	4,27	76,00	80,81	86,25
*****	*******	21	167	58	M	07/08/2018	3,35	4,14	80,00	82,83	83,71

*****	*******	22	167	58	M	20/12/2018	3,26	4,15	78,00	80,85	83,97
*****	*******	28	173	99	F	20/09/2017	2,44	3,42	71,00	66,22	77,19
*****	*******	29	173	91	F	24/05/2019	2,65	3,50	75,00	72,11	79,45
*****	*******	30	173	94	F	24/07/2019	2,39	3,49	68,00	65,18	79,40
*****	*******	30	173	94	F	06/08/2019	2,64	3,43	76,00	72,11	78,16
*****	*******	30	173	93	F	04/09/2019	2,40	3,27	73,00	65,68	74,48
*****	*******	32	172	104	F	21/10/2021	2,34	3,14	74,46	73,55	84,92
*****	*******	32	172	104	F	28/04/2022	2,31	3,53	65,25	72,52	95,55
*****	*******	33	172	104	F	08/09/2022	2,40	3,31	72,53	76,02	89,80
*****	*******	33	172	104	F	01/12/2022	2,24	3,22	69,56	70,88	87,32
*****	*******	33	172	104	F	23/02/2023	2,52	3,44	73,18	79,59	93,20
*****	*******	33	172	104	F	18/05/2023	1,96	3,02	65,10	62,14	81,79
*****	*******	34	172	104	F	10/08/2023	2,35	3,47	67,65	74,77	94,40
*****	*******	34	172	104	F	02/11/2023	2,44	3,38	72,07	77,58	91,94
*****	*******	34	172	104	F	25/01/2024	2,47	3,40	72,52	78,41	92,34
*****	*******	25	175	65	M	04/09/2015	3,34	4,13	80,00	76,52	75,97
*****	*******	25	175	66	M	22/12/2015	3,04	3,91	77,00	69,46	71,81
*****	*******	26	175	65	M	19/03/2016	3,35	4,48	74,00	77,10	82,50
*****	*******	26	175	65	M	15/04/2016	3,02	3,96	76,00	69,38	72,93
*****	*******	26	175	64	M	29/07/2016	3,26	4,37	74,00	74,97	80,47
*****	*******	26	175	67	M	25/11/2016	3,24	4,57	70,00	74,41	84,09
*****	*******	27	175	65	M	24/02/2017	3,55	4,45	79,00	82,05	82,27
*****	*******	27	175	66	M	26/05/2017	3,15	4,23	74,00	72,65	78,16
*****	*******	27	175	64	M	18/08/2017	3,35	4,23	79,00	77,57	78,18
*****	*******	27	175	64	M	17/11/2017	3,04	4,26	71,00	70,51	78,97

NHC	Data_analitica	Eos_Abs	Eos_%	IgE
*****	03/07/2019	0.43	7.7	44.50
*****	29/08/2019	0.38	6.1	191.00
*****	04/01/2020	0.61	12.3	210.00
*****	04/07/2020	0.33	7.5	182.00
*****	30/08/2020	0.03	0.5	
*****	03/09/2020			219.00
*****	27/09/2020	0.02	0.4	
*****	01/10/2020			223.00
*****	25/02/2021	0.03	0.4	56.10
*****	08/08/2021	0.01	0.3	37.40
*****	31/10/2021	0.03	0.7	
*****	04/11/2021			42.60
*****	23/04/2022	0.02	0.3	56.50
*****	09/10/2022	0.03	0.6	49.90
*****	15/01/2023	0.01	0.2	
*****	28/01/2023	0.00	0.0	
*****	01/02/2023			50.00
*****	12/02/2023	0.03	0.4	48.10
*****	25/02/2023	0.03	0.4	
*****	01/03/2023			54.00
*****	12/03/2023	0.08	1.7	42.30
*****	25/03/2023	0.15	2.5	29.60
*****	14/05/2023	0.58	7.3	27.90
*****	11/06/2023	0.56	7.2	28.90
*****	08/10/2023	1.48	18.7	13.20
*****	04/01/2024			19.30
*****	29/05/2019	0.25	3.4	129.00
*****	02/08/2019	0.07	1.0	
*****	04/08/2019			116.00
*****	31/08/2019	0.14	2.0	
*****	01/09/2019			259.00
*****	28/09/2019	0.28	4.1	
*****	29/09/2019			352.00
*****	12/03/2020	0.09	1.2	357.00
*****	23/01/2021	0.03	0.5	
*****	27/01/2021			348.00
*****	05/02/2021	0.03	0.3	
*****	25/06/2022	0.08	1.1	
*****	30/06/2022			197.00
*****	09/07/2022	0.08	1.4	
*****	16/07/2022	0.01	0.2	
*****	06/08/2022	0.00	0.0	
*****	27/08/2022	0.00	0.0	
*****	17/09/2022	0.02	0.5	
*****	08/10/2022	0.00	0.0	
*****	05/11/2022	0.11	2.8	
*****	19/11/2022	0.00	0.0	
*****	23/11/2022			170.00
*****	06/05/2023	0.06	1.7	

*****	10/05/2023			135.00
*****	09/06/2023	0.06	1.4	
*****	07/10/2023	0.06	1.3	
*****	11/10/2023			162.00
*****	02/12/2023	0.05	1.3	
*****	07/05/2015			422
*****	18/11/2015	1.07	14.8	
*****	21/11/2015			1082
*****	19/05/2016	0.36	3.6	
*****	21/05/2016			619
*****	17/11/2016	0.52	8.2	
*****	19/11/2016			363
*****	25/05/2017	0.45	5.2	
*****	27/05/2017			528
*****	18/11/2017	0.15	2.1	
*****	22/11/2017			431
*****	26/05/2018	0.72	8.2	445.00
*****	23/03/2019	0.36	5.5	284.00
*****	07/03/2020	0.99	9.4	
*****	11/03/2020			523.00
*****	17/10/2020	0.97	13.3	
*****	21/10/2020			552.00
*****	10/04/2021	0.02	0.2	
*****	11/04/2021			526.00
*****	03/07/2021	0.67	11.8	
*****	08/07/2021			583.00
*****	24/11/2021	0.19	2.9	
*****	18/12/2021	0.19	2.7	
*****	22/12/2021			464.00
*****	11/06/2022	0.22	3.5	325.00
*****	21/04/2023	0.23	3.6	
*****	23/04/2023			327.00
*****	10/06/2023	0.23	4.1	
*****	15/06/2023			317.00
*****	25/11/2023	0.39	6.0	
*****	29/11/2023			462.00
*****	29/12/2023			287.00
*****	23/07/2016	0.24	3.8	
*****	30/07/2016			406
*****	12/08/2016	0.24	4.1	
*****	13/08/2016			456
*****	30/12/2016	0.27	4.4	
*****	01/01/2017			1448
*****	25/02/2017	0.21	3.3	
*****	30/06/2017	0.27	4.6	
*****	05/07/2017			1334
*****	19/01/2018	0.32	4.3	1002
*****	20/07/2018	0.20	4.5	877.00
*****	11/01/2019	0.37	6.0	787.00
*****	22/03/2019	0.39	7.3	

*****	09/08/2019	0.23	5.0	
*****	10/08/2019			670.00
*****	16/01/2021	0.32	6.8	
*****	20/01/2021			318.00
*****	24/04/2021	0.37	7.3	
*****	29/04/2021			974.00
*****	17/07/2021	0.28	6.7	
*****	18/07/2021			850.00
*****	09/10/2021	0.28	6.7	
*****	10/10/2021			1130.00
*****	27/11/2021	0.47	8.5	
*****	05/02/2022	0.33	5.1	
*****	13/03/2022	0.16	2.0	
*****	26/03/2022	0.16	1.5	
*****	30/03/2022			964.00
*****	15/07/2022	0.32	5.3	
*****	24/09/2022	0.33	7.4	
*****	28/09/2022			958.00
*****	18/12/2022	0.17	2.5	
*****	18/03/2023	0.32	5.2	
*****	17/06/2023	0.25	3.3	
*****	18/06/2023			563.00
*****	21/09/2023	0.19	4.0	
*****	02/12/2023	0.21	3.5	
*****	06/12/2023			673.00
*****	21/09/2014	.3	3.5	
*****	13/11/2014			498
*****	07/05/2015			571
*****	23/10/2015	.4	4.3	
*****	24/10/2015			393
*****	22/04/2016	0.33	2.8	
*****	24/04/2016			447
*****	08/10/2016	0.31	3,00	
*****	13/10/2016			324
*****	03/03/2017	0.38	3.2	
*****	05/03/2017			552
*****	03/06/2017	0.31	2.6	
*****	27/08/2017	0.4	3.1	
*****	31/08/2017			433
*****	15/02/2018			553
*****	14/07/2018	0.48	4.6	
*****	19/09/2018	0.31	2.7	
*****	10/11/2018	0.08	0.7	
*****	15/12/2018	0.29	3.7	381.00
*****	09/03/2019			486.00
*****	20/03/2019	0.34	3.7	
*****	19/05/2019	0.30	2.9	
*****	09/10/2019	0.29	3.1	
*****	14/12/2019	0.30	3.2	
*****	19/12/2019			400.00

*****	14/03/2020	0.27	3.2	
*****	15/03/2020			307.00
*****	27/05/2020	0.34	4.4	
*****	06/06/2020	0.31	4.5	
*****	10/06/2020			388.00
*****	11/11/2020	0.34	4.4	
*****	12/12/2020	0.29	3.8	
*****	16/12/2020			476.00
*****	25/06/2021	0.22	2.7	
*****	30/06/2021			472.00
*****	03/09/2021	0.20	1.9	
*****	16/10/2021	0.31	3.9	
*****	17/10/2021			325.00
*****	10/11/2021	0.31	3.6	
*****	23/04/2022	0.23	2.6	
*****	27/04/2022			480.00
*****	07/01/2023	0.29	3.6	
*****	11/01/2023			231.00
*****	24/06/2023	0.12	1.8	
*****	25/06/2023			323.00
*****	11/07/2023	0.19	2.2	
*****	16/12/2023	0.10	1.5	
*****	20/12/2023			340.00
*****	03/09/2015	.03	.2	
*****	26/09/2015			306
*****	19/03/2016	0.12	1.5	
*****	20/03/2016			434
*****	05/05/2016	0.12	1.5	447
*****	14/09/2016	0.18	2.2	
*****	18/09/2016			417
*****	11/01/2017	0.08	1.3	
*****	15/03/2017	0.13	1.6	
*****	16/03/2017			319
*****	26/08/2017	0.13	1.8	
*****	31/08/2017			356
*****	21/02/2018			342
*****	29/09/2018	0.09	1.0	351.00
*****	25/05/2019	0.07	0.9	255.00
*****	09/11/2019	0.10	1.2	
*****	14/11/2019			445.00
*****	09/05/2020	0.09	1.5	
*****	14/05/2020			314.00
*****	03/10/2020	0.11	1.9	
*****	07/10/2020			343.00
*****	28/11/2020	0.08	1.3	
*****	02/12/2020			300.00
*****	14/01/2021	0.04	0.3	
*****	15/01/2021	0.15	1.8	
*****	16/01/2021	0.14	2.5	
*****	20/01/2021	0.11	2.2	

*****	24/01/2021			203.00
*****	21/02/2021	0.10	1.5	
*****	22/05/2021	0.13	1.8	
*****	26/05/2021			391.00
*****	14/08/2021	0.14	2.2	
*****	15/08/2021			362.00
*****	21/10/2021	0.15	2.2	
*****	29/01/2022	0.11	1.7	
*****	02/02/2022			316.00
*****	30/04/2022	0.11	1.8	
*****	04/05/2022			322.00
*****	15/10/2022	0.12	1.7	
*****	19/10/2022			335.00
*****	01/04/2023	0.15	1.7	
*****	02/04/2023			284.00
*****	16/09/2023	0.12	1.7	
*****	20/09/2023			289.00
*****	06/06/2018	0.04	0.4	243.00
*****	21/11/2018	0.11	1.5	236.00
*****	10/05/2019	0.07	1.0	775.00
*****	14/11/2019	0.14	1.8	
*****	15/11/2019			590.00
*****	09/02/2020	0.06	0.7	
*****	12/02/2020			538.00
*****	05/06/2020	0.09	1.3	
*****	06/06/2020			561.00
*****	11/12/2020			588.00
*****	29/01/2021	0.21	2.8	
*****	13/05/2021	0.04	0.4	
*****	15/05/2021			465.00
*****	05/08/2021	0.11	1.4	
*****	06/08/2021			366.00
*****	29/09/2021	0.09	1.1	
*****	27/10/2021	0.11	1.6	342.00
*****	19/01/2022	0.07	0.7	
*****	20/01/2022			409.00
*****	16/03/2022	0.10	1.4	379.00
*****	13/04/2022	0.14	1.6	
*****	14/04/2022			303.00
*****	13/05/2022	0.07	0.9	
*****	14/05/2022			254.00
*****	03/09/2022	0.09	1.4	
*****	08/09/2022			53.50
*****	25/02/2023	0.26	3.9	45.60
*****	30/06/2023	0.22	2.2	
*****	19/07/2023	0.20	3.2	
*****	01/12/2023	0.20	2.3	32.50
*****	10/12/2023	0.38	1.8	
*****	14/12/2023	0.00	0.0	
*****	17/05/2015			509

*****	11/11/2015	.33	3.4	
*****	12/11/2015			736
*****	13/02/2016	.3	3.2	
*****	18/02/2016			542
*****	27/05/2016	0.38	4.9	
*****	02/06/2016			835
*****	11/12/2016	0.33	3.3	
*****	15/12/2016			743
*****	27/05/2017	0.23	2.7	
*****	28/05/2017			627
*****	25/11/2017	0.25	2.7	
*****	30/11/2017			717
*****	02/06/2018	0.32	3.4	752.00
*****	22/12/2018	0.35	4.2	678.00
*****	22/06/2019	0.36	4.0	
*****	27/06/2019			661.00
*****	14/12/2019	0.32	3.0	
*****	18/12/2019			1307.00
*****	14/03/2020	0.35	3.4	
*****	15/03/2020			951.00
*****	11/10/2020	0.25	2.4	
*****	16/10/2020			819.00
*****	16/01/2021	0.26	3.0	
*****	12/06/2021	0.29	2.9	
*****	16/06/2021			1185.00
*****	18/12/2021	0.30	2.6	
*****	22/12/2021			1239.00
*****	09/06/2022			1364.00
*****	28/01/2023	0.18	1.4	
*****	01/02/2023			1323.00
*****	26/08/2023	0.12	1.6	
*****	27/08/2023			2763.00
*****	11/10/2017	0.15	1.7	62.3
*****	05/04/2018	0.11	1.6	344
*****	27/09/2018	0.08	1.2	401.00
*****	20/03/2019	0.10	1.7	363.00
*****	17/10/2020	0.16	1.9	347.00
*****	16/01/2021	0.06	0.9	
*****	20/01/2021			318.00
*****	01/05/2014	.5	6.4	
*****	18/04/2015			537
*****	18/11/2015	.24	3.6	
*****	20/11/2015			387
*****	20/05/2016	0.77	11.1	
*****	25/05/2016			448
*****	18/12/2016	0.46	7.8	
*****	22/12/2016			340
*****	22/06/2017			551
*****	23/12/2017	0.31	5.4	
*****	30/12/2017			417

*****	09/06/2018	0.16	1.5	331.00
*****	27/04/2019	0.63	8.6	
*****	31/07/2019	0.83	10.2	
*****	02/08/2019			366.00
*****	04/09/2019	0.00	0.0	
*****	05/09/2019			374.00
*****	03/10/2019	0.00	0.0	
*****	04/10/2019			249.00
*****	23/05/2020	0.00	0.0	
*****	27/05/2020			179.00
*****	19/09/2020	0.00	0.0	
*****	23/09/2020			183.00
*****	27/02/2021	0.00	0.0	
*****	03/03/2021			232.00
*****	21/08/2021	0.00	0.0	
*****	26/08/2021			283.00
*****	11/12/2021	0.00	0.0	
*****	15/12/2021			192.00
*****	28/05/2022	0.00	0.0	
*****	01/06/2022			175.00
*****	17/09/2022	0.00	0.0	
*****	21/09/2022			173.00
*****	07/01/2023	0.00	0.0	
*****	12/01/2023			123.00
*****	29/04/2023	0.00	0.0	
*****	04/05/2023			196.00
*****	05/05/2023	0.00	0.0	
*****	13/05/2023	0.00	0.0	
*****	18/05/2023	0.00	0.0	
*****	19/05/2023	0.00	0.0	
*****	21/05/2023	0.00	0.0	
*****	26/08/2023	0.00	0.0	
*****	27/08/2023			40.90
*****	16/12/2023	0.00	0.0	
*****	20/12/2023			47.00
*****	01/10/2014	.53	5.2	
*****	30/11/2014			1384
*****	14/06/2015			1702
*****	12/12/2015	.36	4.9	
*****	17/12/2015			1780
*****	10/03/2017	0.22	3.4	
*****	11/03/2017			1554
*****	13/08/2017			1312
*****	27/01/2018	0.28	4.1	
*****	02/02/2018			1783
*****	14/07/2018	0.13	1.5	813.00
*****	09/02/2019	0.12	1.4	899.00
*****	29/03/2019	0.43	4.3	
*****	13/07/2019	0.26	2.6	
*****	18/07/2019			611.00

*****	12/10/2019	0.01	0.1	
*****	16/10/2019			823.00
*****	18/01/2020	0.13	1.9	
*****	22/01/2020			861.00
*****	23/05/2020	0.11	1.0	
*****	27/05/2020			732.00
*****	20/09/2020			713.00
*****	27/02/2021	0.29	3.3	
*****	03/03/2021			760.00
*****	10/09/2021	0.27	3.8	
*****	11/09/2021			638.00
*****	19/10/2021	0.16	1.6	
*****	25/12/2021	0.31	4.9	
*****	29/12/2021			405.00
*****	14/04/2022	0.14	1.3	
*****	14/05/2022	0.01	0.1	
*****	18/05/2022			480.00
*****	29/10/2022	0.44	5.0	
*****	02/11/2022			431.00
*****	22/11/2022	0.00	0.0	
*****	05/02/2023	0.20	2.8	
*****	09/02/2023			298.00
*****	18/02/2023	0.16	2.1	
*****	23/02/2023			345.00
*****	04/03/2023	0.16	2.3	
*****	08/03/2023			378.00
*****	01/04/2023	0.17	2.0	
*****	05/04/2023			295.00
*****	15/04/2023	0.23	2.7	
*****	19/04/2023			256.00
*****	30/04/2023	0.10	1.2	
*****	05/05/2023			216.00
*****	27/05/2023	0.35	3.9	
*****	31/05/2023			191.00
*****	24/06/2023	0.29	3.0	79.60
*****	22/07/2023	0.15	2.0	
*****	27/07/2023			50.20
*****	19/08/2023	0.38	5.1	
*****	20/08/2023			36.10
*****	11/11/2023	0.20	2.3	
*****	15/11/2023			33.80
*****	27/08/2015			226
*****	02/03/2016	0.32	5.2	
*****	03/03/2016			246
*****	31/08/2016	0.57	9.6	
*****	02/09/2016			314
*****	29/01/2017	0.01	0.02	
*****	01/02/2017			286
*****	26/07/2017	0.33	5.1	
*****	28/07/2017			421

*****	02/02/2018			725
*****	21/07/2018	0.27	5.2	402.00
*****	26/01/2019	0.31	5.3	409.00
*****	27/07/2019	0.38	6.4	
*****	31/07/2019			366.00
*****	27/06/2020	0.40	6.5	
*****	01/07/2020			419.00
*****	24/12/2020	0.33	6.1	
*****	25/12/2020			433.00
*****	25/06/2021	0.47	8.2	
*****	30/06/2021			354.00
*****	25/12/2021	0.27	4.7	
*****	29/12/2021			374.00
*****	19/03/2022	0.30	5.3	
*****	23/03/2022			389.00
*****	10/09/2022	0.50	8.3	388.00
*****	25/02/2023	0.25	5.3	
*****	26/02/2023			902.00
*****	19/08/2023	0.43	7.7	416.00
*****	02/07/2015			835
*****	07/01/2016	0.18	2.3	
*****	09/01/2016			921
*****	24/07/2016	0.1	1.1	
*****	30/07/2016			908
*****	25/01/2017	0.16	2.1	
*****	27/01/2017			909
*****	12/07/2017	0.19	2.4	1062
*****	15/02/2018			949
*****	22/09/2018	0.11	1.4	778.00
*****	11/05/2019	0.11	1.3	813.00
*****	30/11/2019	0.10	1.2	
*****	04/12/2019			940.00
*****	06/06/2020	0.07	0.8	
*****	10/06/2020			658.00
*****	05/12/2020	0.10	1.3	
*****	11/12/2020			580.00
*****	22/05/2021	0.06	0.7	
*****	26/05/2021			554.00
*****	19/02/2022	0.09	1.1	
*****	23/02/2022			532.00
*****	06/08/2022	0.06	0.9	
*****	10/08/2022			471.00
*****	15/04/2023	0.02	0.2	
*****	19/04/2023			660.00
*****	07/10/2023	0.07	1.0	519.00
*****	14/03/2015			132
*****	10/06/2015	.29	4.1	
*****	24/09/2015			97.7
*****	24/03/2016	.25	3.6	
*****	25/03/2016			92

*****	29/05/2016	0.21	2.8	
*****	02/10/2016	0.2	2.8	88.6
*****	26/04/2017	0.31	4.4	
*****	28/04/2017			107
*****	21/10/2017	0.22	3.4	
*****	25/10/2017			102
*****	21/02/2018			102
*****	29/09/2018	0.28	3.8	158.00
*****	17/10/2018	0.33	3.5	
*****	30/03/2019	0.31	4.6	257.00
*****	14/09/2019	0.28	4.5	200.00
*****	31/12/2019	0.22	2.6	
*****	06/06/2020	0.29	3.2	
*****	10/06/2020			187.00
*****	13/06/2020	0.37	3.7	
*****	17/11/2021	0.24	3.2	
*****	23/04/2022	0.23	2.8	
*****	27/04/2022			163.00
*****	01/10/2022	0.32	3.9	
*****	05/10/2022			192.00
*****	18/03/2023	0.29	3.1	
*****	22/03/2023			203.00
*****	02/09/2023	0.33	4.5	
*****	07/09/2023			189.00
*****	29/05/2014	.1	.7	
*****	26/10/2014			1132
*****	09/04/2015			1365
*****	26/08/2015			2044
*****	12/02/2016	1.12	11,00	
*****	14/02/2016			3363
*****	04/06/2016	0.5	4.4	
*****	03/08/2016	0.31	2.7	
*****	05/08/2016			1867
*****	21/12/2016	0.44	3.9	
*****	22/12/2016			1885
*****	14/06/2017	1.54	13.4	
*****	18/06/2017			2404
*****	03/09/2017	2.04	18.3	
*****	02/12/2017	3.17	24.1	
*****	06/12/2017			2673
*****	28/03/2018	0,00	0,00	
*****	12/05/2018	0.51	5.0	4792.00
*****	29/09/2018	0.43	3.9	2559.00
*****	23/02/2019	0.27	0.39	2214.00
*****	07/04/2019	0.16	1.4	
*****	24/08/2019	0.26	2.3	
*****	25/08/2019			1532.00
*****	22/09/2019	0.21	1.7	
*****	12/02/2020	0.12	0.9	
*****	20/02/2020			1599.00

*****	09/07/2020	0.19	1.7	
*****	10/10/2020	0.49	4.7	
*****	15/10/2020			2439.00
*****	01/01/2021	0.34	3.2	
*****	19/02/2021	0.11	0.8	
*****	24/04/2021	0.27	2.3	
*****	29/04/2021			1521.00
*****	07/05/2021	0.25	2.7	
*****	04/06/2021	0.16	1.4	
*****	13/06/2021	0.93	7.5	
*****	24/09/2021	0.36	2.7	
*****	16/10/2021	0.62	5.6	2573.00
*****	12/11/2021	0.94	7.1	
*****	20/11/2021	0.09	0.5	
*****	15/01/2022	1.07	8.4	
*****	16/01/2022			2162.00
*****	23/01/2022	1.02	8.8	
*****	26/01/2022	0.61	4.9	
*****	27/04/2022	0.96	7.2	
*****	08/05/2022	0.69	6.6	
*****	24/06/2022	0.28	1.4	
*****	27/06/2022	1.13	10.3	
*****	02/07/2022	0.37	2.3	
*****	03/07/2022	0.25	2.1	
*****	06/07/2022	0.16	0.33	
*****	09/07/2022	0.08	0.5	
*****	10/07/2022	0.14	1.0	
*****	13/07/2022	0.04	0.4	
*****	16/07/2022	0.06	0.6	
*****	19/07/2022	0.08	0.8	
*****	21/07/2022	0.08	0.6	
*****	23/07/2022	0.21	1.6	
*****	27/07/2022	0.29	2.8	
*****	03/08/2022	0.25	2.2	
*****	14/06/2015			93.7
*****	18/07/2015	.57	6.8	
*****	24/09/2015	.16	1.8	
*****	27/11/2015	.33	4.2	
*****	28/11/2015			122
*****	06/02/2016	0.56	4.7	
*****	27/04/2016	0.23	2.3	
*****	29/06/2016	0.05	0.6	
*****	31/07/2016	0.07	1.1	
*****	18/09/2016	0.13	1.4	
*****	26/11/2016	0.15	1,00	
*****	19/02/2017	0.17	2,00	
*****	05/03/2017	0.13	1.2	
*****	08/03/2017			90.5
*****	19/03/2017	0,00	0,00	
*****	25/03/2017	0,00	0,00	

*****	31/03/2017	0.01	0.1	
*****	10/05/2017	0.05	0.6	
*****	17/06/2017	0.21	2.9	
*****	18/06/2017			54.7
*****	25/06/2017	0.2	2.6	
*****	21/09/2017	0.23	3.1	
*****	27/09/2017			68.5
*****	02/11/2017	0.2	2.3	
*****	24/01/2018	0.34	4.2	
*****	07/06/2018	0.20	2.4	
*****	15/09/2018	0.69	9.0	122.00
*****	16/11/2018	0.10	1.4	
*****	23/01/2019	0.17	1.8	
*****	11/05/2019	0.39	4.4	100.00
*****	15/06/2019	0.33	4.4	
*****	28/09/2019	0.41	6.3	
*****	18/10/2019	0.26	4.3	
*****	15/02/2020	0.35	5.3	
*****	19/02/2020			79.30
*****	15/03/2020	0.37	4.7	
*****	04/07/2020	0.43	6.4	
*****	08/07/2020			83.90
*****	20/11/2020	0.27	3.6	
*****	09/01/2021	0.27	4.1	
*****	13/01/2021			86.60
*****	07/02/2021	0.33	2.6	
*****	26/02/2021	0.29	4.4	
*****	10/04/2021	0.21	2.3	
*****	11/04/2021			98.30
*****	03/06/2021	0.16	2.9	
*****	04/06/2021	0.05	0.9	
*****	09/06/2021	0.10	1.3	
*****	11/06/2021	0.21	3.1	
*****	24/07/2021			62.70
*****	20/11/2021	0.24	3.1	
*****	24/11/2021	0.00	0.0	
*****	23/04/2022	0.23	3.8	
*****	27/04/2022			50.20
*****	01/09/2022	0.09	1.3	
*****	08/10/2022	0.08	1.0	
*****	12/10/2022			95.50
*****	10/11/2022	0.04	0.5	
*****	13/11/2022	0.00	0.0	
*****	15/11/2022	0.00	0.0	
*****	17/11/2022	0.00	0.0	
*****	18/11/2022	0.00	0.0	
*****	19/11/2022	0.00	0.0	
*****	20/11/2022	0.00	0.0	
*****	23/11/2022	0.02	0.1	
*****	25/11/2022	0.02	0.1	

*****	27/11/2022	0.02	0.1	
*****	30/11/2022	0.04	0.4	
*****	03/12/2022	0.06	0.9	
*****	07/12/2022	0.00	0.0	
*****	25/03/2023	0.04	0.5	
*****	29/03/2023			48.90
*****	16/04/2023	0.03	0.4	
*****	20/04/2023			54.60
*****	29/04/2023	0.01	0.1	
*****	04/05/2023			47.70
*****	13/05/2023	0.04	0.5	
*****	14/05/2023			32.00
*****	10/06/2023	0.05	0.7	
*****	14/06/2023			25.50
*****	24/06/2023	0.02	0.3	
*****	25/06/2023			18.00
*****	08/07/2023	0.02	0.3	
*****	12/07/2023			13.80
*****	23/09/2023	0.02	0.3	
*****	27/09/2023			6.86
*****	22/10/2023	0.05	0.7	
*****	26/10/2023			7.23
*****	28/09/2014	.66	17.5	
*****	22/01/2015			411
*****	22/07/2015			286
*****	20/12/2015	.28	2.6	
*****	10/01/2016	.41	9.2	
*****	14/01/2016			278
*****	08/05/2016	0.55	12.9	
*****	10/07/2016	0.77	18.4	
*****	13/07/2016			436
*****	28/01/2017	0.11	1.9	
*****	29/01/2017			351
*****	05/03/2017	1.35	29,00	
*****	23/04/2017	0.11	2.8	
*****	28/04/2017			401
*****	21/05/2017	0.08	2.2	
*****	24/05/2017			431
*****	19/08/2017	0.1	2.7	144
*****	15/11/2017	0.05	1,00	
*****	17/11/2017			217
*****	18/02/2018	0.12	3.3	
*****	21/02/2018			313
*****	15/04/2018	0.05	0.8	
*****	08/06/2018	0.01	0.1	222.00
*****	09/09/2018	0.03	0.9	
*****	28/10/2018	0.06	1.5	356.00
*****	24/02/2019	0.08	2.5	
*****	19/05/2019	0.05	1.4	
*****	20/10/2019	0.08	2.2	

*****	24/10/2019			435.00
*****	16/11/2019	0.08	2.1	
*****	15/03/2020	0.04	1.3	
*****	18/03/2020			343.00
*****	21/06/2020	0.02	0.6	
*****	25/06/2020			410.00
*****	20/09/2020	0.07	1.9	
*****	23/09/2020			476.00
*****	07/10/2020	0.01	0.1	
*****	13/12/2020	0.06	1.6	
*****	16/12/2020			243.00
*****	06/06/2021	0.05	1.3	
*****	09/06/2021			318.00
*****	29/08/2021	0.07	1.4	
*****	03/09/2021			334.00
*****	21/11/2021	0.08	2.0	
*****	24/11/2021			361.00
*****	05/06/2022	0.08	2.0	
*****	09/06/2022			1285.00
*****	28/08/2022	0.07	1.2	
*****	31/08/2022			643.00
*****	12/02/2023	0.06	1.5	
*****	15/02/2023			565.00
*****	02/07/2023	0.00	0.0	
*****	07/07/2023			446.00
*****	23/11/2023	0.06	1.6	
*****	24/11/2023			412.00
*****	20/09/2017	0.11	1.9	
*****	18/12/2017	0.12	1.3	
*****	18/07/2018	0.12	2.0	121.00
*****	27/07/2014	.3	.31	
*****	11/01/2015	.31	3.2	
*****	11/03/2015			450
*****	25/10/2015	.31	.35	
*****	29/10/2015			485
*****	03/06/2016	0.29	3.5	460
*****	15/02/2017	0.33	3.3	
*****	16/02/2017			441
*****	28/10/2017	0.31	2.9	
*****	01/11/2017			447
*****	07/03/2018			340
*****	27/04/2019	0.24	2.0	587.00
*****	09/10/2019	0.24	2.7	
*****	10/10/2019			449.00
*****	13/12/2019	0.24	1.8	
*****	10/10/2020	0.29	2.5	
*****	15/10/2020			185.00
*****	17/04/2021	0.31	2.6	
*****	21/04/2021			193.00
*****	13/11/2021	0.45	5.2	

*****	14/11/2021			232.00
*****	11/12/2021	0.14	1.4	
*****	15/12/2021			215.00
*****	29/01/2022	0.15	1.4	
*****	02/02/2022			202.00
*****	26/02/2022	0.20	1.8	
*****	02/03/2022			196.00
*****	06/08/2022	0.34	3.6	
*****	10/08/2022			229.00
*****	21/01/2023	0.42	4.1	
*****	26/01/2023			126.00
*****	13/05/2023	0.34	3.7	
*****	18/05/2023			212.00
*****	05/08/2023	0.24	2.4	
*****	10/08/2023			180.00
*****	05/06/2013	.33	3.2	
*****	26/02/2016	0.17	2.2	
*****	28/02/2016			8.61
*****	19/10/2016	0.24	2.8	
*****	21/10/2016			58.4
*****	14/04/2017	0.22	2.9	
*****	20/04/2017			50.1
*****	29/09/2017	0.21	2.3	
*****	01/10/2017			46.8
*****	29/09/2018	0.14	1.3	55.90
*****	16/03/2019	0.13	1.3	54.10
*****	28/09/2019	0.21	1.5	
*****	02/10/2019			48.60
*****	21/03/2020	0.18	1.6	
*****	22/03/2020			48.70
*****	12/09/2020	0.10	1.0	
*****	16/09/2020			44.10
*****	05/12/2020	0.11	1.2	
*****	11/12/2020			60.00
*****	22/05/2021	0.14	1.5	
*****	26/05/2021			56.20
*****	23/10/2021	0.10	1.0	
*****	27/10/2021			48.20
*****	23/04/2022	0.08	0.9	
*****	27/04/2022			57.10
*****	09/10/2022	0.14	1.5	
*****	13/10/2022			65.20
*****	16/04/2023	0.10	1.2	
*****	20/04/2023			61.10
*****	08/10/2023	0.16	1.8	
*****	12/10/2023			39.80
*****	12/11/2023	0.09	1.3	
*****	27/01/2013	.68	8.9	
*****	08/12/2013	.1	1.1	
*****	22/06/2014	.62	9.8	

*****	30/07/2014	.56	8.8	
*****	25/01/2015			844
*****	02/08/2015			901
*****	31/08/2015	.44	5.8	
*****	12/02/2016	.05	0.05	636
*****	12/06/2016	0.33	4.5	
*****	17/12/2016	0.16	2.4	
*****	21/12/2016			543
*****	13/04/2017	0.22	3,00	406
*****	07/05/2017	0.39	5.6	
*****	01/11/2017	0.42	5.5	
*****	04/11/2017			730
*****	07/04/2018	0.53	6,00	
*****	20/07/2018	0.29	3.0	755.00
*****	26/10/2018	0.24	3.4	
*****	07/04/2019	0.34	3.5	
*****	04/05/2019	0.53	5.5	827.00
*****	08/11/2019	0.39	4.4	
*****	20/05/2020	0.38	4.8	
*****	04/07/2020	0.34	4.0	
*****	08/07/2020			1088.00
*****	12/11/2020	0.63	7.1	
*****	30/01/2021	0.44	6.2	
*****	03/02/2021			1450.00
*****	19/05/2021	0.11	1.2	
*****	29/05/2021	0.41	5.0	
*****	01/01/2022	0.35	4.7	
*****	02/01/2022			1367.00
*****	18/06/2022	0.28	3.6	
*****	22/06/2022			1131.00
*****	10/11/2022	0.28	2.4	
*****	18/12/2022	0.37	5.3	
*****	22/12/2022			889.00
*****	28/05/2023	0.32	4.1	
*****	31/05/2023	0.24	3.7	
*****	01/06/2023			1486.00
*****	12/11/2023	0.28	4.3	
*****	15/11/2023			1227.00
*****	14/03/2013			1515
*****	15/09/2013	.4	4.7	
*****	16/01/2014	.24	2.4	
*****	18/07/2014	.34	4.1	
*****	23/01/2015	.37	3.9	
*****	24/01/2015			1714
*****	07/06/2015	.44	4.5	
*****	24/06/2015	.31	3.4	
*****	03/07/2015	.41	4.2	
*****	07/08/2015	.31	3.3	
*****	25/09/2015	.3	3.5	
*****	01/10/2015			1473

*****	16/12/2015	0.36	4.4	
*****	23/02/2016	.16	1.9	
*****	07/05/2016	0.26	2.7	
*****	19/05/2016	0.19	2,00	
*****	21/05/2016	0.17	2.3	
*****	25/05/2016			1132
*****	03/07/2016	0.15	1.4	
*****	04/07/2016	0.19	2,00	
*****	29/08/2016	0.25	3.1	
*****	15/09/2016	0.23	3.5	
*****	18/09/2016			1022
*****	07/12/2016	0.13	1.7	
*****	18/12/2016	0.19	2.2	
*****	18/03/2017	0.26	3,00	
*****	17/06/2017	0.27	4.3	
*****	18/06/2017			1039
*****	10/03/2018	0.31	6.2	
*****	14/03/2018			1563
*****	14/06/2018	0.30	3.9	
*****	28/06/2018	0.10	1.0	
*****	24/11/2018	0.44	7.1	1742.00
*****	15/06/2019	0.15	2.0	1876.00
*****	01/09/2019	0.12	1.6	
*****	13/10/2019	0.02	0.04	
*****	30/10/2019	0.18	1.3	
*****	11/01/2020	0.09	1.0	
*****	15/01/2020			1092.00
*****	17/04/2020	0.07	0.6	
*****	19/04/2020	0.04	0.3	
*****	27/06/2020	0.10	0.7	
*****	11/07/2020	0.17	0.8	
*****	15/07/2020	0.38	5.8	
*****	20/09/2020	0.40	5.1	
*****	23/09/2020			1745.00
*****	27/03/2021	0.22	2.8	
*****	31/03/2021			2955.00
*****	10/05/2021	0.22	3.3	
*****	25/12/2021	0.31	4.2	
*****	29/12/2021			1848.00
*****	09/01/2022	0.47	10.3	
*****	14/05/2022	0.24	3.9	
*****	18/05/2022			1877.00
*****	23/06/2022	0.26	4.2	
*****	11/12/2022	0.14	2.3	
*****	15/12/2022			1395.00
*****	27/03/2023	0.14	1.7	
*****	28/03/2023	0.14	3.0	
*****	06/04/2023	0.29	5.5	
*****	28/04/2023	0.26	4.6	
*****	29/04/2023	0.19	2.9	

*****	30/04/2023	0.24	2.2	
*****	06/05/2023	0.22	3.3	
*****	11/06/2023	0.07	0.7	
*****	15/06/2023			1252.00
*****	28/07/2023	0.04	0.6	
*****	30/07/2023	0.03	0.3	
*****	31/07/2023	0.08	1.0	
*****	02/08/2023	0.12	1.8	
*****	04/08/2023	0.10	2.1	
*****	09/08/2023	0.18	2.4	
*****	10/08/2023	0.25	3.8	
*****	11/08/2023	0.20	2.8	
*****	20/09/2023	0.05	0.9	
*****	05/11/2023	0.06	0.9	
*****	09/11/2023			1516.00
*****	03/10/2013	.09	1.1	
*****	20/03/2014	.15	1.9	
*****	04/10/2014	.25	2.9	
*****	10/04/2015			932
*****	18/10/2015			763
*****	04/11/2015	.23	2.6	
*****	14/02/2016	0.29	2.7	
*****	14/04/2016			946
*****	12/05/2016	0.25	2.5	
*****	13/08/2016	0.3	3.2	
*****	09/10/2016	0.25	2,00	
*****	13/10/2016			593
*****	01/03/2017	0.28	2.7	
*****	09/04/2017	0.19	1.9	
*****	13/04/2017			706
*****	17/06/2017	0.35	3.2	
*****	03/09/2017	0.32	2.7	
*****	06/12/2017	0.12	1.1	
*****	21/04/2018	0.29	3.1	
*****	23/02/2019	0.26	2.5	
*****	04/07/2019	0.26	2.7	
*****	12/06/2020	0.12	1.6	
*****	03/10/2020	0.32	3.4	
*****	04/08/2021	0.29	2.2	
*****	07/08/2022	0.41	3.9	
*****	20/04/2013			721
*****	22/09/2013			785
*****	14/03/2015			747
*****	10/09/2015			702
*****	12/03/2016	0.22	1.7	
*****	13/03/2016			777
*****	10/06/2016	0.15	1.7	
*****	10/09/2016	0.19	1.8	
*****	14/09/2016			863
*****	04/03/2017	0.23	2.4	

*****	05/03/2017			1009
*****	02/09/2017	0.21	2.1	880
*****	28/02/2018			1066
*****	29/09/2018	0.14	1.4	689.00
*****	04/05/2019	0.12	1.1	871.00
*****	16/11/2019	0.15	1.6	
*****	20/11/2019			966.00
*****	13/06/2020	0.07	0.6	
*****	24/12/2020	0.15	1.6	
*****	30/12/2020			500.00
*****	04/09/2021	0.13	1.4	
*****	28/05/2022	0.08	0.9	
*****	01/06/2022			444.00
*****	12/11/2022	0.18	1.9	
*****	16/11/2022			534.00
*****	06/05/2023	0.07	0.6	448.00
*****	14/02/2013	.21	2.7	
*****	04/05/2013	.24	3.6	
*****	11/12/2013	.39	5.6	
*****	07/02/2014	.34	4.2	
*****	10/05/2014	.38	5.4	
*****	22/05/2014	.36	5.6	
*****	20/11/2014	.3	3,00	
*****	23/11/2014	.13	1.2	
*****	06/12/2014	.36	4.5	
*****	07/12/2014			220
*****	15/01/2015			266
*****	31/05/2015	.38	4.4	
*****	04/07/2015	.36	5.5	
*****	08/07/2015			280
*****	15/10/2015	.22	3.2	
*****	19/10/2015	.05	.6	
*****	31/10/2015	.17	2.2	
*****	03/12/2015	.18	2.6	
*****	15/01/2016	.24	3.3	
*****	17/01/2016			222
*****	09/07/2016	0.02	0.3	
*****	13/07/2016			264
*****	11/09/2016	0.26	3.7	
*****	05/11/2016	0.26	4,00	309
*****	11/01/2017	0.36	5.6	
*****	19/01/2017			385
*****	29/03/2017	0.22	3,00	
*****	12/07/2017	0.38	5.1	
*****	14/07/2017			377
*****	03/02/2018	0.27	3.2	
*****	07/02/2018			435
*****	15/09/2018	0.30	3.7	407.00
*****	23/02/2019	0.28	3.4	474.00
*****	03/07/2019	0.75	7.1	

*****	04/07/2019			703.00
*****	15/08/2019	0.10	1.3	
*****	16/08/2019			277.00
*****	08/09/2019	0.09	1.2	
*****	14/09/2019			228.00
*****	04/01/2020	0.08	1.3	
*****	05/01/2020			399.00
*****	03/07/2020	0.00	0.0	
*****	04/07/2020			240.00
*****	24/12/2020	0.07	1.0	
*****	25/12/2020			145.00
*****	08/05/2021	0.11	1.5	
*****	13/05/2021			148.00
*****	27/11/2021	0.05	0.7	
*****	02/12/2021			124.00
*****	22/01/2022	0.10	1.2	
*****	26/01/2022			493.00
*****	19/02/2022	0.05	0.5	
*****	23/02/2022			429.00
*****	18/06/2022	0.06	0.7	
*****	22/06/2022			378.00
*****	03/12/2022	0.06	0.6	
*****	07/12/2022			354.00
*****	07/01/2023	0.07	0.6	
*****	11/01/2023			277.00
*****	21/01/2023	0.06	0.6	
*****	25/01/2023			306.00
*****	04/02/2023	0.12	1.2	
*****	08/02/2023			245.00
*****	18/02/2023	0.14	1.3	
*****	23/02/2023			263.00
*****	04/03/2023	0.15	1.5	
*****	08/03/2023			196.00
*****	01/04/2023	0.23	2.6	
*****	05/04/2023			119.00
*****	30/04/2023	0.28	2.8	
*****	05/05/2023			63.80
*****	03/06/2023	0.30	3.4	
*****	07/06/2023			44.00
*****	01/07/2023	0.38	4.1	
*****	05/07/2023			34.60
*****	27/04/2013			475
*****	25/05/2013	.02	.2	
*****	14/03/2014	.19	3,00	
*****	08/06/2014			429
*****	13/12/2014			622
*****	28/06/2015			315
*****	21/10/2015	.03	.3	
*****	23/12/2015	0.06	0.5	
*****	25/12/2015			255

*****	31/03/2016	0,00	0,00	
*****	01/04/2016			299
*****	28/01/2017	0.16	2.5	
*****	29/01/2017			476
*****	27/03/2017	0.24	3.7	
*****	11/08/2017	0.38	4.9	354
*****	21/03/2018	0.17	2.4	
*****	23/03/2018			554
*****	28/02/2019	0.02	0.2	554.00
*****	11/04/2019	0.05	0.7	
*****	11/07/2019	0.10	1.2	
*****	27/09/2019	0.23	2.8	
*****	05/03/2021	0.26	3.5	
*****	20/04/2021	0.35	4.3	
*****	25/01/2023	0.30	3.7	
*****	23/02/2023			118.00
*****	12/06/2015	.17	2.1	
*****	14/06/2015			124
*****	27/04/2017	0.32	3.6	
*****	29/04/2017			227
*****	30/08/2017	0.36	0.45	524
*****	25/01/2018	0.08	1.5	541
*****	29/06/2018	0.23	3.4	427.00
*****	28/07/2018	0.34	5.0	
*****	28/10/2018	0.25	4.3	
*****	01/03/2019	0.23	2.2	
*****	20/03/2019	0.25	4.2	414.00
*****	07/07/2019	0.15	2.6	
*****	10/07/2019			307.00
*****	04/01/2020	1.14	14.7	
*****	05/01/2020			456.00
*****	16/08/2020	0.44	5.3	
*****	20/08/2020			525.00
*****	10/10/2020	0.04	0.4	
*****	15/10/2020			676.00
*****	04/12/2020	0.05	0.7	
*****	11/12/2020			303.00
*****	26/02/2021	0.05	0.5	
*****	28/02/2021			284.00
*****	17/04/2021	0.00	0.0	
*****	11/06/2021	0.13	2.9	
*****	12/06/2021			451.00
*****	08/08/2021	0.08	1.2	
*****	11/08/2021			292.00
*****	07/10/2021	0.10	1.3	
*****	05/11/2021	0.09	1.4	
*****	06/11/2021			286.00
*****	04/12/2021	0.25	5.4	
*****	05/12/2021			170.00
*****	02/01/2022	0.34	5.0	

*****	05/01/2022			167.00
*****	16/03/2022	0.13	1.7	
*****	18/03/2022			118.00
*****	02/06/2022	1.40	20.1	
*****	01/12/2022	0.47	7.0	
*****	02/12/2022			56.50
*****	01/06/2023	0.08	0.7	
*****	04/06/2023	0.01	0.1	
*****	07/06/2023	0.04	0.4	
*****	10/08/2023	0.05	0.9	
*****	11/08/2023			17.50
*****	05/10/2023	0.00	0.0	
*****	07/10/2023			16.30
*****	30/11/2013	.11	1.1	
*****	24/07/2014	.12	1.8	
*****	13/02/2015	.19	3,00	
*****	07/02/2016	0.15	1.9	
*****	31/05/2016	0.14	1.6	
*****	30/03/2017	0.18	2.7	
*****	11/10/2017	0.11	1.1	
*****	01/11/2017	0.16	1.1	
*****	08/11/2017			274
*****	05/12/2017	0.08	0.7	
*****	04/03/2018	0.11	1.2	
*****	08/03/2018			65.2
*****	17/03/2018	0.1	1.7	
*****	24/06/2018	0.18	2.2	
*****	08/09/2018	0.16	2.3	246.00
*****	23/02/2019	0.11	1.4	
*****	27/03/2019	0.29	5.1	
*****	14/04/2019	0.16	2.7	
*****	19/05/2019	0.13	2.1	366.00
*****	28/11/2019	0.15	2.2	309.00
*****	23/03/2020	0.00	0.0	
*****	11/01/2014	.31	3.7	
*****	14/03/2014	.38	4.2	
*****	19/03/2016	0.6	6.4	
*****	20/03/2016			388
*****	06/05/2017	0.63	7,00	
*****	18/10/2017	0.54	7.3	
*****	19/10/2017			785
*****	18/03/2018			989
*****	15/09/2018	0.23	2.5	1069.00
*****	09/03/2019	0.30	3.5	1026.00
*****	07/08/2019	0.31	3.0	
*****	07/09/2019	0.57	7.0	
*****	14/09/2019			836.00
*****	05/02/2020	0.58	6.6	
*****	07/03/2020	0.24	2.7	
*****	11/03/2020			856.00

*****	26/09/2020	0.20	2.0	
*****	30/09/2020			1292.00
*****	20/03/2021	0.29	3.2	
*****	11/09/2021	0.44	5.9	833.00
*****	26/02/2022	0.24	2.8	
*****	02/03/2022			1005.00
*****	17/09/2022	0.14	1.4	
*****	21/09/2022			964.00
*****	18/12/2022	0.30	3.0	
*****	22/12/2022			1253.00
*****	28/05/2023	0.24	2.6	
*****	01/06/2023			1176.00
*****	22/10/2023	0.45	5.0	
*****	17/12/2023	0.23	2.1	
*****	21/12/2023			947.00
*****	21/06/2013			439
*****	09/07/2014	.23	4.6	
*****	10/07/2014	.19	3.4	
*****	09/01/2015	0.35	5.8	
*****	15/01/2015			158
*****	28/06/2015			110
*****	23/12/2015	0.19	3.5	
*****	25/12/2015			114
*****	11/03/2016	.11	1.1	
*****	25/06/2016	0.21	3.6	
*****	29/06/2016			89.2
*****	17/12/2016	0.29	4.2	
*****	21/12/2016			133
*****	02/06/2017	0.25	4.2	
*****	04/06/2017			115
*****	11/11/2017	0.16	2.6	
*****	15/11/2017			112
*****	05/05/2018	0.11	1.4	
*****	12/05/2018			98
*****	01/09/2018	0.20	3.1	84.70
*****	27/10/2018	0.26	4.4	80.60
*****	01/06/2019	0.16	2.5	91.20
*****	07/12/2019	0.31	3.7	
*****	13/12/2019			106.00
*****	27/06/2020	0.21	3.8	
*****	01/07/2020			133.00
*****	16/01/2021	0.24	3.9	
*****	20/01/2021			174.00
*****	01/04/2021	0.26	4.0	
*****	04/04/2021	0.19	2.7	
*****	09/04/2021	0.29	4.7	
*****	15/04/2021			94.60
*****	03/07/2021	0.21	3.4	
*****	08/07/2021			111.00
*****	21/10/2021	0.19	3.1	

*****	22/10/2021			828.00
*****	18/11/2021	0.04	0.7	636.00
*****	16/12/2021	0.04	0.7	
*****	17/12/2021			430.00
*****	04/06/2022	0.05	0.8	
*****	05/06/2022			48.30
*****	11/03/2023	0.04	0.8	
*****	15/03/2023			49.20
*****	10/04/2013	.25	4.2	
*****	19/12/2013	.17	3.5	
*****	05/06/2014	.22	4.8	
*****	27/07/2014	.05	.5	
*****	20/08/2014	.23	4.3	
*****	28/11/2014	.21	4.4	
*****	18/01/2015			299
*****	28/03/2015	.19	3.1	
*****	12/04/2015			276
*****	08/07/2015			198
*****	25/12/2015	.3	5.7	
*****	31/12/2015			214
*****	11/06/2016	0.24	4.8	
*****	12/06/2016			223
*****	26/08/2016	0.14	1.8	
*****	23/02/2017	0.18	2.8	
*****	01/04/2017	0.21	3.5	
*****	25/10/2019	0.24	3.8	
*****	05/12/2019	0.00	0.0	
*****	02/05/2021	0.00	0.0	
*****	30/05/2013			367
*****	13/11/2013	.21	2.6	
*****	26/12/2013			395
*****	15/01/2015			416
*****	09/07/2015			341
*****	06/02/2016	0.19	3.3	372
*****	29/07/2016	0.22	4.1	
*****	31/07/2016			344
*****	20/01/2017	0.27	5.7	254
*****	12/10/2018	0.31	5.3	
*****	28/07/2021	0.19	2.4	
*****	29/07/2021	0.18	3.2	
*****	14/03/2013	.34	3.1	
*****	15/09/2013			878
*****	23/11/2013	.17	1.3	
*****	06/03/2014			796
*****	11/05/2014	.5	4.4	
*****	28/06/2014	.21	1.3	
*****	25/09/2014	.6	4.9	
*****	02/10/2015			835
*****	16/10/2015	.16	1.5	
*****	25/12/2015			947

*****	05/03/2016	0.19	1.9	
*****	22/06/2016	0.36	2.8	
*****	24/06/2016			898
*****	15/12/2016	0.01	0.1	
*****	11/01/2017	0.13	0.7	
*****	17/01/2017	0.01	0,00	
*****	19/01/2017	0.02	0.1	
*****	27/01/2017	0,00	0,00	
*****	08/02/2017	0,00	0,00	
*****	02/04/2017	0.08	0.8	
*****	21/06/2017	0.12	1.1	
*****	22/06/2017			247
*****	23/12/2017	0.02	0.2	
*****	30/12/2017			510
*****	10/02/2018	0.32	2.4	
*****	23/02/2018	0.1	0.8	
*****	03/05/2018	0.21	2,00	
*****	21/06/2018	0.23	1.8	635.00
*****	03/08/2018	0.56	5.4	
*****	21/10/2018	0.60	6.2	
*****	29/11/2018	0.16	1.6	
*****	12/01/2019	0.51	3.9	783.00
*****	01/02/2019	0.17	1.3	
*****	01/03/2019	0.16	1.7	
*****	06/04/2019	0.11	1.0	
*****	27/07/2019	0.73	7.6	
*****	31/07/2019			572.00
*****	27/10/2019	0.60	5.9	
*****	10/11/2019	0.07	0.7	
*****	30/11/2019	0.25	2.4	
*****	18/12/2019	0.00	0.0	
*****	05/01/2020	0.27	3.2	
*****	19/01/2020	0.55	5.5	
*****	23/01/2020			834.00
*****	30/01/2020	0.05	0.5	
*****	15/02/2020	0.06	0.6	
*****	16/02/2020			589.00
*****	24/05/2020	0.14	1.3	
*****	28/05/2020			228.00
*****	11/07/2020	0.03	0.2	
*****	06/09/2020	0.04	0.3	
*****	10/09/2020			292.00
*****	25/09/2020	0.01	0.1	
*****	18/02/2021	0.06	0.6	
*****	02/04/2021	0.02	0.2	
*****	08/04/2021			229.00
*****	29/04/2021	0.03	0.3	
*****	16/05/2021	0.04	0.4	
*****	27/08/2021	0.10	1.0	
*****	11/09/2021	0.08	0.7	

*****	15/09/2021			607.00
*****	17/10/2021	0.04	0.3	
*****	18/10/2021	0.02	0.2	
*****	19/10/2021	0.04	0.4	
*****	20/10/2021	0.03	0.3	
*****	24/10/2021	0.06	0.6	
*****	09/02/2022	0.00	0.0	
*****	10/02/2022	0.00	0.01	
*****	17/02/2022	0.04	0.3	
*****	23/02/2022	0.00	0.0	
*****	02/03/2022	0.01	0.1	
*****	05/03/2022	0.01	0.1	
*****	06/03/2022	0.00	0.0	
*****	08/03/2022	0.00	0.0	
*****	09/03/2022	0.01	0.1	
*****	11/03/2022	0.03	0.4	
*****	13/03/2022	0.00	0.0	
*****	17/03/2022	0.02	0.3	
*****	23/03/2022	0.00	0.0	
*****	30/03/2022	0.00	0.0	
*****	31/03/2022	0.03	0.2	
*****	02/04/2022	0.05	0.5	
*****	06/04/2022	0.01	0.1	
*****	08/04/2022	0.01	0.1	
*****	13/04/2022	0.02	0.1	
*****	14/04/2022	0.08	0.5	
*****	06/12/2013	.16	3.8	
*****	21/12/2014			484
*****	24/01/2015			424
*****	12/08/2015			383
*****	24/01/2016	.17	3.6	
*****	28/01/2016			434
*****	27/08/2016	0.21	5,00	
*****	28/08/2016			343
*****	22/02/2017	0.16	3.8	256
*****	09/09/2017	0.39	11.1	
*****	10/09/2017			289
*****	24/02/2018	0.01	0.4	
*****	28/02/2018			267
*****	19/09/2018	0.00	0.0	230.00
*****	13/01/2019	0.00	0.0	218.00
*****	06/06/2019	0.01	0.3	256.00
*****	23/11/2019	0.00	0.0	
*****	24/11/2019			248.00
*****	29/05/2020	0.01	0.3	188.00
*****	24/09/2020	0.00	0.0	
*****	26/09/2020			254.00
*****	09/04/2021	0.00	0.0	
*****	10/04/2021			117.00
*****	03/07/2021	0.00	0.0	

*****	08/07/2021			97.10
*****	25/09/2021	0.00	0.0	
*****	26/09/2021			106.00
*****	12/03/2022	0.00	0.0	
*****	13/03/2022			133.00
*****	04/09/2022	0.13	3.0	
*****	08/09/2022			199.00
*****	18/03/2023	0.30	5.6	141.00
*****	27/09/2023	0.15	3.5	
*****	30/09/2023			151.00
*****	25/05/2014			189
*****	30/11/2014			214
*****	24/05/2015			211
*****	06/12/2015	.16	2.5	
*****	11/12/2015			221
*****	12/06/2016	0.12	1.2	
*****	16/06/2016			257
*****	03/12/2016	0.18	2.6	
*****	07/12/2016			226
*****	03/06/2017	0.43	5.2	
*****	04/06/2017			350
*****	19/07/2017	0.23	3.2	
*****	02/12/2017	0.25	3.5	
*****	06/12/2017			329
*****	15/02/2018	0.13	1.4	
*****	07/07/2018	0.13	2.2	194.00
*****	12/01/2019	0.11	1.0	227.00
*****	16/03/2019	0.05	0.5	
*****	06/07/2019	0.08	1.1	
*****	10/07/2019			178.00
*****	05/01/2020	0.19	2.8	
*****	10/01/2020			191.00
*****	20/06/2020	0.19	2.2	
*****	24/06/2020			260.00
*****	24/07/2020	0.07	0.9	
*****	24/10/2020	0.08	1.4	
*****	09/01/2021	0.07	1.0	
*****	06/03/2021	0.02	0.3	
*****	10/03/2021			264.00
*****	28/03/2021	0.03	0.4	
*****	30/05/2021	0.06	0.9	
*****	12/06/2021	0.04	0.5	
*****	16/06/2021			131.00
*****	14/07/2021	0.11	1.7	
*****	28/10/2021	0.06	0.7	
*****	29/10/2021	0.04	0.7	
*****	31/10/2021	0.07	1.0	
*****	04/11/2021	0.09	1.8	
*****	05/11/2021	0.12	2.3	
*****	11/11/2021	0.08	1.3	

*****	17/11/2021	0.05	0.9	
*****	25/12/2021	0.04	0.7	
*****	29/12/2021			79.40
*****	23/03/2022	0.04	0.8	
*****	11/06/2022	0.03	0.6	
*****	15/06/2022			71.50
*****	07/08/2022	0.04	0.6	
*****	18/09/2022	0.09	1.8	
*****	20/11/2022	0.03	0.5	
*****	03/12/2022	0.04	0.6	
*****	07/12/2022			166.00
*****	20/05/2023	0.14	2.3	
*****	21/05/2023			169.00
*****	19/07/2023	0.09	1.0	
*****	21/07/2023	0.11	1.7	
*****	16/08/2023	0.08	1.8	
*****	02/09/2023	0.05	0.7	
*****	09/09/2023	0.07	1.2	
*****	04/11/2023	0.04	0.9	
*****	05/11/2023			182.00
*****	16/08/2013	.16	2.8	
*****	08/10/2013	.01	.1	
*****	05/07/2016	0.09	1.2	
*****	19/02/2017	0.11	1.6	
*****	23/02/2017			540
*****	22/06/2017	0.12	2.1	
*****	30/08/2018	0.10	1.2	373.00
*****	22/09/2018	0.10	1.6	290.00
*****	09/03/2019			1210.00
*****	10/07/2019	0.09	1.6	
*****	11/07/2019			950.00
*****	10/01/2020	0.09	1.3	
*****	11/01/2020			962.00
*****	24/02/2020	0.04	0.4	
*****	27/08/2020	0.13	2.0	1213.00
*****	20/02/2021	0.12	2.7	1236.00
*****	07/08/2021	0.18	2.8	999.00
*****	23/01/2022	0.15	2.4	
*****	29/01/2022	0.16	2.5	
*****	02/02/2022			1309.00
*****	10/04/2022			1131.00
*****	06/11/2022	0.08	1.3	
*****	10/11/2022			1229.00
*****	23/04/2023	0.18	3.2	
*****	27/04/2023			1345.00
*****	10/05/2023	0.09	1.0	
*****	12/05/2023	0.08	1.3	
*****	15/10/2023	0.25	4.2	
*****	19/10/2023			1036.00
*****	16/04/2015			547

*****	18/10/2015			852
*****	28/11/2015	.6	6.3	
*****	20/01/2016	.06	.4	
*****	21/01/2016	.01	.17	
*****	22/01/2016	0,00	0,00	
*****	24/01/2016	.01	.1	
*****	29/01/2016	.24	1.8	
*****	03/02/2016	.33	3.3	
*****	16/04/2016	0.67	6.3	
*****	17/04/2016			414
*****	02/10/2016	0.58	5.3	
*****	03/10/2016	0.69	5.4	
*****	06/10/2016	0,00	0.07	
*****	07/10/2016	0.48	4.3	
*****	08/10/2016	0.12	1.1	
*****	09/10/2016	0.36	2.7	
*****	12/10/2016	0.43	5,00	
*****	15/10/2016	0.72	5.1	
*****	19/10/2016	0.48	3.8	
*****	24/10/2016	0.03	0.32	
*****	25/10/2016	0,00	0,00	
*****	26/10/2016	0,00	0,00	
*****	27/10/2016	0,00	0,00	
*****	28/10/2016	0,00	0,00	
*****	29/10/2016	0,00	0,00	
*****	30/10/2016	0,00	0,00	
*****	31/10/2016	0,00	0,00	
*****	01/11/2016	0,00	0,00	
*****	04/11/2016	0.03	0.1	
*****	05/11/2016	0.03	0.1	
*****	12/11/2016	0.09	0.7	
*****	17/11/2016	0.02	0.2	
*****	19/12/2016	0.12	0.8	
*****	28/01/2017	0.56	4.6	
*****	29/01/2017			198
*****	30/04/2017	2.04	14.3	
*****	22/10/2017	1.04	8.8	
*****	25/10/2017			571
*****	24/03/2018	0.79	5.6	
*****	30/03/2018			603
*****	24/05/2018	0.94	8.0	
*****	15/07/2018	0.75	6.6	
*****	17/01/2019	0.17	1.7	
*****	13/12/2015	.04	.3	
*****	17/12/2015			131
*****	15/07/2016	0.79	7.9	
*****	17/07/2016			167
*****	24/07/2016	1.34	10.9	
*****	30/07/2016			136
*****	23/12/2016	2.33	26.8	

*****	24/12/2016			754
*****	22/09/2017	1.13	17.4	
*****	27/09/2017			563
*****	18/01/2018	0.54	5.9	
*****	20/01/2018			637
*****	24/03/2018	1,00	14.4	
*****	30/03/2018			645
*****	29/09/2018	0.99	14.8	520.00
*****	27/10/2018	0.15	2.1	539.00
*****	13/03/2019	0.13	1.9	169.00
*****	07/09/2019	0.39	6.1	
*****	08/09/2019			97.90
*****	10/06/2020	0.09	1.4	
*****	11/06/2020			123.00
*****	12/09/2020	0.07	1.4	
*****	16/09/2020			114.00
*****	10/04/2021	0.03	0.5	
*****	14/04/2021			164.00
*****	11/09/2021	0.07	1.3	
*****	12/09/2021			107.00
*****	26/02/2022	0.04	0.7	
*****	02/03/2022			105.00
*****	10/09/2022	0.02	0.3	
*****	14/09/2022			106.00
*****	03/12/2022	0.03	0.4	
*****	17/12/2022	0.04	0.6	
*****	21/12/2022			74.20
*****	31/12/2022	0.06	1.0	
*****	04/01/2023			72.40
*****	14/01/2023	0.09	1.3	
*****	18/01/2023			64.60
*****	28/01/2023	0.26	4.0	
*****	01/02/2023			68.40
*****	11/02/2023	0.23	3.2	
*****	15/02/2023			85.30
*****	25/02/2023	0.19	3.4	
*****	01/03/2023			71.70
*****	11/03/2023	0.76	9.8	
*****	15/03/2023			63.70
*****	15/04/2023	1.40	15.0	
*****	19/04/2023			60.60
*****	20/05/2023	2.01	28.5	50.90
*****	17/06/2023	0.71	6.3	
*****	18/06/2023			30.80
*****	08/07/2023	2.14	25.3	
*****	12/07/2023			25.30
*****	02/09/2023	2.00	24.6	25.50
*****	25/11/2023	1.20	17.8	
*****	29/11/2023			33.30
*****	04/09/2013	.07	.4	

*****	05/09/2013	.2	1.2	
*****	26/03/2017	0.22	1.5	
*****	18/07/2017	0.07	0.4	
*****	27/07/2017	0.02	0.1	
*****	30/07/2017			526
*****	30/01/2018	0,00	0,00	
*****	06/04/2018	0.15	1.3	
*****	31/05/2018	0.38	4.9	768.00
*****	17/10/2018	0.10	1.0	619.00
*****	25/11/2018	1.18	11.7	
*****	09/01/2019	0.98	10.3	670.00
*****	01/05/2019	0.64	8.3	
*****	31/05/2019	0.70	8.0	1036.00
*****	10/08/2019	0.39	4.2	
*****	11/08/2019			738.00
*****	15/09/2019	0.00	0.0	
*****	18/09/2019			827.00
*****	20/10/2019	0.00	0.0	
*****	24/10/2019			853.00
*****	19/02/2020	0.14	1.9	
*****	20/02/2020			485.00
*****	20/06/2020	0.00	0.0	
*****	24/06/2020			497.00
*****	19/09/2020	0.00	0.0	
*****	28/01/2021	0.00	0.0	
*****	31/03/2021	0.00	0.0	
*****	11/06/2021	0.00	0.0	
*****	12/06/2021			624.00
*****	17/07/2021	0.00	0.0	
*****	18/07/2021			1891.00
*****	14/08/2021	0.00	0.0	
*****	15/08/2021			1930.00
*****	09/04/2022	0.00	0.0	
*****	13/04/2022			2347.00
*****	24/09/2022	0.00	0.0	
*****	28/09/2022			2163.00
*****	14/01/2023	0.00	0.0	
*****	28/01/2023	0.00	0.0	
*****	01/02/2023			1577.00
*****	11/02/2023	0.00	0.0	
*****	15/02/2023	0.00	0.0	1992.00
*****	11/03/2023	0.00	0.0	
*****	15/03/2023			< 2.00
*****	25/03/2023	0.00	0.0	
*****	29/03/2023			1233.00
*****	20/05/2023	0.00	0.0	
*****	24/05/2023			604.00
*****	24/06/2023	0.00	0.0	
*****	25/06/2023			331.00
*****	12/09/2023	0.59	3.3	

*****	13/09/2023	0.56	4.8	
*****	16/12/2023	0.46	3.4	
*****	20/12/2023			176.00
*****	25/04/2013	.03	.5	
*****	27/03/2014	.05	1,00	
*****	20/02/2015			375
*****	22/08/2015			377
*****	04/11/2015	.15	2.5	
*****	13/02/2016	0.11	1.8	
*****	14/02/2016			407
*****	30/07/2016	0.08	1.4	
*****	03/08/2016			411
*****	05/08/2016			365
*****	25/09/2016	0,00	0,00	
*****	19/01/2017	0.05	0.8	
*****	20/01/2017			354
*****	02/03/2017	0,00	0,00	
*****	03/03/2017	0,00	0.01	
*****	04/03/2017	0.18	1.7	
*****	05/03/2017	0.32	4.1	
*****	10/03/2017	0.37	6.3	
*****	15/03/2017	1.49	25,00	
*****	29/06/2017	0.1	2.2	
*****	01/07/2017			293
*****	23/09/2017	0.11	2.3	
*****	27/09/2017			301
*****	19/01/2018	0.02	0.3	
*****	22/02/2018	0.06	1,00	
*****	13/03/2018	0.08	1.4	
*****	08/09/2018	0.09	1.4	388.00
*****	09/03/2019	0.04	0.6	446.00
*****	07/09/2019	0.04	0.7	
*****	14/09/2019			279.00
*****	13/08/2020	0.07	1.2	
*****	14/08/2020	0.05	0.8	
*****	16/08/2020	0.04	0.8	
*****	20/08/2020	0.36	6.9	
*****	23/08/2020	0.07	0.8	
*****	30/08/2020	0.22	3.7	
*****	18/11/2020	0.04	0.2	
*****	19/11/2020	0.00	0.24	
*****	20/11/2020	0.00	0.0	
*****	21/11/2020	0.04	0.6	
*****	25/11/2020	0.15	1.8	
*****	29/11/2020	0.12	1.5	
*****	11/12/2020	0.03	0.6	
*****	26/03/2021	0.07	0.3	
*****	27/03/2021	0.00	0.0	
*****	16/09/2015	.17	2.8	
*****	18/09/2015			189

*****	09/03/2016	0.14	2.7	171
*****	31/08/2016	0.13	2.2	
*****	01/09/2016			179
*****	22/02/2017	0.13	1.8	
*****	23/02/2017			171
*****	04/11/2017	0.16	1.8	
*****	08/11/2017			198
*****	22/09/2018	0.08	1.0	129.00
*****	25/05/2019	0.07	0.8	136.00
*****	16/11/2019	0.13	1.8	
*****	20/11/2019			185.00
*****	19/09/2020	0.12	1.4	
*****	23/09/2020			149.00
*****	13/03/2021	0.08	1.0	
*****	17/03/2021			161.00
*****	28/08/2021	0.12	1.6	
*****	01/09/2021			88.10
*****	12/02/2022	0.09	1.1	
*****	16/02/2022			110.00
*****	06/08/2022	0.17	2.5	
*****	10/08/2022			102.00
*****	30/11/2014	.1	1.3	
*****	03/12/2014			221
*****	02/07/2015			147
*****	20/12/2015	0.12	1.5	
*****	25/12/2015			162
*****	17/04/2016	0.11	0.7	
*****	21/04/2016	0.24	2.3	
*****	27/04/2016	0.28	2.7	
*****	28/05/2016	0.18	2.1	
*****	04/06/2016	0.22	2.8	
*****	16/10/2016	0.13	1.7	
*****	19/10/2016			158
*****	22/01/2017	0.17	2.2	
*****	25/01/2017			121
*****	23/04/2017	0.15	1.6	
*****	28/04/2017			128
*****	13/05/2017	0,00	0,00	
*****	14/05/2017	0.01	0.08	
*****	28/10/2017	0.12	1.4	
*****	01/11/2017			194
*****	15/01/2018	0.01	0.1	
*****	21/04/2018	0.1	1.4	
*****	26/04/2018			333
*****	06/10/2018	0.16	1.9	269.00
*****	28/02/2019	0.17	1.9	166.00
*****	06/04/2019	0.11	1.3	157.00
*****	11/05/2019	0.17	2.0	
*****	12/10/2019	0.11	1.3	
*****	16/10/2019			163.00

*****	11/01/2020	0.12	1.3	
*****	15/01/2020			151.00
*****	16/03/2013			167
*****	23/10/2013	.25	3,00	
*****	01/05/2015			718
*****	29/05/2015			725
*****	23/10/2015			643
*****	24/04/2016	0.35	4.7	
*****	28/04/2016			836
*****	28/10/2016	0.3	3.4	
*****	06/04/2017	0.29	2.9	
*****	07/04/2017			671
*****	28/09/2017	0.29	3.3	
*****	01/10/2017			707
*****	17/03/2018	0.25	2.6	
*****	21/03/2018			745
*****	06/10/2018	0.27	2.8	812.00
*****	06/04/2019	0.24	2.3	854.00
*****	19/10/2019	0.31	3.5	
*****	24/10/2019			1053.00
*****	13/10/2023	0.25	2.4	
*****	18/10/2023			379.00
*****	21/03/2014	.19	1.9	
*****	03/06/2014	.02	.3	
*****	09/06/2014	.16	2.6	
*****	12/09/2014	.07	.8	
*****	21/09/2014			536
*****	20/03/2015			414
*****	03/10/2015	.24	3.7	
*****	09/10/2015			465
*****	10/03/2016	0.22	2.9	
*****	11/03/2016			381
*****	26/08/2016	0.47	4.9	
*****	28/08/2016			510
*****	04/03/2017	0.26	2.7	
*****	05/03/2017			497
*****	01/10/2017	0.21	2.4	
*****	04/10/2017			285
*****	19/01/2018	0.26	2.1	
*****	28/04/2018	0.14	1.4	
*****	04/05/2018			574
*****	13/10/2018	0.31	3.7	444.00
*****	19/10/2018	0.21	2.0	
*****	04/05/2019	0.17	2.1	504.00
*****	10/10/2019	0.14	1.6	
*****	11/10/2019			376.00
*****	02/11/2019	0.13	1.5	
*****	06/11/2019			355.00
*****	23/05/2020	0.00	0.0	
*****	27/05/2020			281.00

*****	17/10/2020	0.01	0.2	
*****	18/10/2020			247.00
*****	10/07/2021	0.11	1.3	
*****	14/07/2021			225.00
*****	01/01/2022	0.29	2.8	
*****	02/01/2022			349.00
*****	25/06/2022	0.22	1.9	
*****	30/06/2022			290.00
*****	17/12/2022	0.24	2.7	
*****	21/12/2022			281.00
*****	11/03/2023	0.11	1.2	
*****	15/03/2023			326.00
*****	26/08/2023	0.18	1.9	
*****	27/08/2023			240.00
*****	01/02/2014			2817
*****	19/07/2014			2031
*****	04/02/2015	.65	8.3	
*****	20/02/2015			1778
*****	15/08/2015			1405
*****	12/02/2016			1435
*****	31/03/2016	.91	7.3	
*****	11/08/2016	0.82	11.4	
*****	12/08/2016			1528
*****	13/08/2016			1557
*****	02/11/2017	1.1	12,00	
*****	05/11/2017			762
*****	11/04/2014	.05	.6	
*****	08/10/2014	.02	.2	
*****	17/10/2014	.06	.3	
*****	07/05/2017	0.18	1.6	
*****	22/06/2017	0.25	4.1	
*****	17/05/2019	0.05	0.7	203.00
*****	19/04/2020	0.07	0.9	
*****	01/03/2014	.29	3.7	
*****	29/04/2015			450
*****	08/11/2015	.45	6.5	
*****	12/11/2015			495
*****	19/03/2016	.41	4.5	
*****	12/08/2016	0.33	5,00	
*****	13/08/2016			509
*****	14/08/2016			516
*****	13/03/2017	0.28	3.9	
*****	16/03/2017	0.02	0.3	
*****	17/03/2017			300
*****	13/07/2017	0.26	4.7	
*****	14/07/2017			643
*****	11/10/2017	0.35	4.3	
*****	15/10/2017			413
*****	06/01/2018	0.2	3.2	
*****	10/01/2018			657

*****	16/06/2018	0.23	2.6	
*****	28/07/2018	0.16	2.1	523.00
*****	26/01/2019	0.18	3.0	286.00
*****	27/07/2019	0.26	3.8	
*****	31/07/2019			294.00
*****	29/09/2019	0.22	3.1	
*****	30/09/2019	0.24	4.5	
*****	25/01/2020	0.37	4.6	
*****	29/01/2020			451.00
*****	13/08/2020	0.19	2.1	
*****	01/10/2020	0.10	2.2	
*****	25/11/2020	0.23	2.9	
*****	17/03/2021	0.41	4.9	
*****	21/03/2021			433.00
*****	13/06/2021	0.19	1.9	
*****	10/07/2021	0.12	1.4	320.00
*****	09/10/2021	0.10	1.0	
*****	15/10/2021			414.00
*****	06/11/2021	0.06	0.7	245.00
*****	04/12/2021	0.06	0.9	112.00
*****	02/04/2022	0.10	1.4	
*****	06/04/2022			122.00
*****	23/06/2022	0.02	0.3	
*****	24/09/2022	0.04	0.5	
*****	28/09/2022			125.00
*****	31/12/2022	0.02	0.3	
*****	26/02/2023	0.15	2.2	
*****	02/03/2023			76.80
*****	27/08/2023	0.31	5.0	
*****	30/08/2023			124.00
*****	23/10/2023	0.06	1.2	
*****	19/11/2023	0.07	1.1	
*****	23/11/2023			140.00
*****	03/02/2015	.03	.2	
*****	15/03/2015	0,00	0,00	
*****	26/03/2015	.26	2.6	
*****	30/04/2015	.24	2.7	
*****	22/05/2015	0,00	0,00	
*****	14/06/2015	.18	1.7	
*****	17/06/2015			313
*****	20/06/2015	.01	.1	
*****	24/06/2015	.1	1,00	
*****	14/08/2015	.06	.3	
*****	24/08/2015	.01	.1	
*****	11/09/2015	.13	1.2	
*****	24/10/2015	0,00	0,00	
*****	03/11/2015	0,00	0,00	
*****	06/11/2015	.03	.2	
*****	12/11/2015	.05	.6	
*****	04/01/2016	.01	.1	

*****	26/04/2016	0,00	0,00
*****	11/05/2016	0,00	0,00
*****	07/06/2016	0,00	0,00
*****	06/07/2016	0,00	0,00
*****	24/07/2016	0.03	0.2
*****	25/07/2016	0,00	0,00
*****	28/07/2016	0.02	0.2
*****	03/08/2016	0.03	0.3
*****	06/08/2016	0.03	0.3
*****	18/08/2016	0.08	0.6
*****	18/09/2016	0.36	1.7
*****	21/09/2016	0.72	8.2
*****	24/12/2016	0,00	0,00
*****	25/12/2016	0.01	0.1
*****	21/01/2017	0.01	0,00
*****	22/01/2017	0,00	0,00
*****	25/01/2017	0.01	0.1
*****	26/01/2017	0,00	0,00
*****	05/02/2017	0.05	0.4
*****	08/03/2017	0.02	0.1
*****	11/04/2017	0,00	0,00
*****	16/04/2017	0,00	0,00
*****	20/04/2017	0,00	0,00
*****	26/04/2017	0,00	0,00
*****	04/05/2017	0,00	0,00
*****	25/05/2017	0,00	0,00
*****	27/05/2017	0,00	0,00
*****	01/06/2017	0.02	0.2
*****	03/06/2017	0.03	0.2
*****	11/06/2017	0.05	0.5
*****	22/06/2017	0,00	0,00
*****	28/06/2017	0.01	0.1
*****	20/08/2017	0,00	0,00
*****	21/08/2017	0,00	0,00
*****	22/08/2017	0,00	0,00
*****	23/08/2017	0,00	0,00
*****	24/08/2017	0,00	0,00
*****	25/08/2017	0,00	0,00
*****	26/08/2017	0,00	0,00
*****	27/08/2017	0,00	0,00
*****	28/08/2017	0,00	0,00
*****	01/09/2017	0.01	0.1
*****	03/09/2017	0.01	0.1
*****	07/09/2017	0.01	0.1
*****	15/09/2017	0.05	0.4
*****	20/09/2017	0.06	0.6
*****	27/09/2017	0.21	2.5
*****	04/10/2017	0.12	1.6
*****	15/10/2017	0.36	3.8
*****	02/11/2017	0.22	2.6

*****	15/11/2017	0.23	3.2
*****	20/11/2017	0.13	1.4
*****	22/11/2017	0.32	3.6
*****	09/01/2018	0.01	0.1
*****	10/03/2018	0.01	0.1
*****	11/03/2018	0,00	0,00
*****	13/03/2018	0,00	0,00
*****	14/03/2018	0,00	0,00
*****	15/03/2018	0.01	0.1
*****	16/03/2018	0,00	0,00
*****	18/03/2018	0.01	0.1
*****	28/03/2018	0.04	0.4
*****	09/08/2018	0.01	0.1
*****	11/08/2018	0.00	0.0
*****	15/01/2019	0.00	0.0
*****	22/01/2019	0.00	0.0
*****	23/01/2019	0.01	0.04
*****	25/01/2019	0.01	0.1
*****	01/02/2019	0.03	0.2
*****	02/05/2019	0.21	1.3
*****	11/06/2019	0.00	0.0
*****	05/09/2019	0.19	0.7
*****	06/09/2019	0.04	0.2
*****	10/09/2019	0.00	0.0
*****	12/10/2019	0.00	0.0
*****	16/10/2019	0.02	0.1
*****	26/10/2019	0.04	0.2
*****	27/10/2019	0.01	0.2
*****	28/10/2019	0.03	0.1
*****	29/10/2019	0.03	0.2
*****	31/10/2019	0.01	0.1
*****	02/11/2019	0.01	0.1
*****	03/11/2019	0.00	0.0
*****	04/11/2019	0.01	0.1
*****	05/11/2019	0.00	0.0
*****	07/11/2019	0.04	0.3
*****	10/11/2019	0.06	0.6
*****	13/11/2019	0.03	0.4
*****	16/11/2019	0.07	0.7
*****	21/11/2019	0.10	0.8
*****	26/11/2019	0.03	0.1
*****	27/11/2019	0.10	0.5
*****	29/11/2019	0.08	0.7
*****	01/12/2019	0.18	0.7
*****	04/12/2019	0.16	1.7
*****	11/12/2019	0.15	1.3
*****	23/12/2019	0.39	2.7
*****	24/12/2019	0.25	0.33
*****	26/01/2020	0.05	0.3
*****	29/05/2020	0.02	0.09

*****	30/05/2020	0.01	0.1	
*****	31/05/2020	0.03	0.4	
*****	01/06/2020	0.03	0.4	
*****	05/06/2020	0.08	0.8	
*****	10/06/2020	0.15	1.3	
*****	18/06/2020	0.27	0.28	
*****	19/06/2020	0.25	2.4	
*****	15/08/2020	0.08	0.5	
*****	16/08/2020	0.09	0.7	
*****	19/08/2020	0.13	1.6	
*****	29/08/2020	0.12	0.6	
*****	13/11/2020	0.03	0.2	
*****	25/02/2021	0.23	1.2	
*****	26/02/2021	0.01	0.1	
*****	27/02/2021	0.02	0.2	
*****	19/05/2021	0.02	0.1	
*****	16/09/2021	0.06	0.4	
*****	22/09/2021	0.29	1.6	
*****	14/04/2022	0.23	1.8	
*****	05/11/2023	0.04	0.3	
*****	31/01/2014	.06	1.2	
*****	05/02/2015	.08	2,00	
*****	08/02/2015			868
*****	26/08/2015			666
*****	06/05/2016	0.07	1.8	
*****	17/12/2016	0.05	1.2	747
*****	17/10/2021	0.13	2.9	
*****	30/10/2021			427.00
*****	06/07/2017	0.29	3.6	
*****	12/07/2017			4.26
*****	16/12/2017	0.25	3.2	5.41
*****	09/06/2018	0.27	4.9	4.85
*****	19/06/2013	.52	5.2	
*****	23/07/2014	.28	3.7	
*****	06/01/2016	.42	3.9	
*****	04/03/2016	0.45	4.9	
*****	05/03/2016			134
*****	13/04/2016	0.41	5.6	
*****	30/07/2016	0.34	4,00	
*****	03/08/2016			587
*****	03/09/2016	0.37	4.1	
*****	26/01/2017	0.29	2.8	
*****	28/01/2017			469
*****	08/04/2017	0.31	2.9	
*****	22/07/2017	0.31	3.2	
*****	26/07/2017			436
*****	22/09/2017	0.41	4.5	
*****	12/01/2018	0.27	2.8	
*****	14/01/2018			386
*****	21/03/2018	0.3	3,00	

*****	23/03/2018			435
*****	13/06/2018	0.31	3.4	316.00
*****	07/11/2018	0.25	2.3	344.00
*****	15/02/2019			353.00
*****	30/08/2019	0.22	2.3	
*****	31/08/2019			366.00
*****	06/03/2020	0.15	1.6	
*****	07/03/2020			356.00
*****	23/08/2020	0.35	3.5	
*****	26/08/2020			2586.00
*****	09/01/2021	0.23	2.5	
*****	13/01/2021			944.00
*****	04/07/2021	0.22	2.2	
*****	08/07/2021			470.00
*****	26/09/2021	0.24	2.4	
*****	30/09/2021			546.00
*****	09/04/2022	0.32	2.9	
*****	13/04/2022			228.00
*****	02/10/2022	0.34	3.2	
*****	06/10/2022			212.00
*****	05/03/2023	0.22	2.7	
*****	09/03/2023			681.00
*****	20/08/2023	0.33	3.0	
*****	23/08/2023			582.00
*****	15/04/2016	0.12	2.1	
*****	22/04/2016			323
*****	15/07/2016	0.06	1.2	
*****	17/07/2016			260
*****	04/12/2016	0.11	1.7	
*****	09/12/2016			1039
*****	02/06/2017	0.09	0.9	
*****	04/06/2017			1102
*****	23/12/2017	0.14	1.8	
*****	30/12/2017			1027
*****	28/06/2018	0.14	2.4	523.00
*****	22/12/2018	0.15	1.8	818.00
*****	29/06/2019	0.08	1.7	
*****	30/06/2019			538.00
*****	21/12/2019	0.10	1.9	
*****	25/12/2019			798.00
*****	23/05/2020	0.16	2.8	
*****	27/05/2020			671.00
*****	20/06/2020	0.08	1.6	
*****	25/06/2020			713.00
*****	24/12/2020	0.07	1.2	
*****	30/12/2020			641.00
*****	19/06/2021	0.07	1.4	
*****	23/06/2021			533.00
*****	25/12/2021	0.03	0.5	
*****	29/12/2021			515.00

*****	18/06/2022	0.06	1.1	
*****	22/06/2022			546.00
*****	17/12/2022	0.12	1.9	
*****	21/12/2022			501.00
*****	17/06/2023	0.11	1.8	
*****	18/06/2023			413.00
*****	09/09/2023	0.08	1.2	
*****	14/09/2023			525.00
*****	07/10/2023	0.03	0.4	
*****	11/10/2023			402.00
*****	04/11/2023	0.02	0.2	
*****	08/11/2023			473.00
*****	02/12/2023	0.05	0.9	
*****	06/12/2023			361.00
*****	26/01/2014			181
*****	26/11/2014			267
*****	21/05/2015			255
*****	06/11/2015	.3	4.8	
*****	08/11/2015			284
*****	14/04/2016			265
*****	25/09/2016	0.52	7.6	
*****	30/09/2016			258
*****	19/03/2017	0.3	3.8	
*****	22/03/2017			217
*****	16/09/2017	0.19	2.4	
*****	20/09/2017			235
*****	27/10/2018	0.49	6.7	294.00
*****	01/08/2019	0.08	0.6	
*****	22/08/2019	0.13	1.3	
*****	09/11/2019	0.57	5.9	
*****	14/11/2019			361.00
*****	26/02/2020	0.11	1.2	
*****	27/03/2021	0.06	0.6	
*****	31/03/2021			321.00
*****	20/04/2021	0.05	0.3	
*****	18/01/2022	0.22	1.2	
*****	20/01/2022	0.14	1.2	
*****	23/01/2022	0.10	0.8	
*****	24/01/2022	0.25	1.9	
*****	25/01/2022	0.14	1.2	
*****	06/02/2022	0.16	1.9	
*****	09/02/2022	0.02	0.1	
*****	13/02/2022	0.28	3.1	
*****	19/02/2022	0.26	3.1	
*****	25/03/2022	0.06	0.3	
*****	26/03/2022	0.00	0.0	
*****	27/03/2022	0.12	0.8	382.00
*****	01/04/2022	0.42	3.4	
*****	03/04/2022	0.15	1.4	
*****	06/04/2022	0.07	0.6	

*****	08/04/2022	0.08	0.5	
*****	10/04/2022	0.01	0.1	
*****	13/04/2022	0.00	0.0	
*****	21/04/2022	0.04	0.5	
*****	26/04/2022	0.06	0.6	
*****	30/04/2022	0.08	0.9	
*****	31/05/2022	0.03	0.2	
*****	04/06/2022	0.00	0.0	
*****	12/06/2022	0.13	0.9	
*****	17/06/2022	0.12	0.7	
*****	19/06/2022	0.29	1.7	
*****	01/07/2022	0.55	7.9	
*****	03/07/2022	0.37	4.8	
*****	06/07/2022	0.36	8.2	
*****	08/07/2022	0.40	6.1	
*****	13/07/2022	0.82	10.3	
*****	14/07/2022	1.08	12.3	
*****	16/07/2022	1.57	16.2	
*****	17/07/2022	0.50	4.8	
*****	18/07/2022	1.38	14.4	
*****	22/07/2022	3.23	26.1	
*****	23/07/2022	5.18	37.6	
*****	27/07/2022	2.85	24.2	
*****	30/07/2022	5.89	46.4	
*****	04/08/2022	0.78	6.6	
*****	07/08/2022	1.57	15.8	
*****	10/08/2022	3.18	26.0	
*****	02/09/2022	0.41	5.3	
*****	15/09/2022	1.21	16.3	
*****	23/09/2022	1.05	12.3	
*****	28/09/2022	1.06	13.4	
*****	21/10/2022	2.35	34.1	
*****	02/11/2022	2.22	16.9	
*****	04/02/2016	0.18	3.2	457
*****	02/02/2017	0.17	2.9	
*****	27/09/2014	.32	7.6	
*****	11/08/2017	0.35	7.5	464
*****	22/10/2015	.33	5.1	
*****	25/11/2015	.28	4.3	
*****	20/05/2016	0.44	6.2	
*****	25/05/2016			1603
*****	07/05/2017	0.09	1.3	
*****	08/02/2018	0.37	5.6	
*****	10/02/2018			889
*****	29/08/2020	0.11	1.3	
*****	02/09/2020			3501.00
*****	30/01/2021	0.16	2.2	
*****	03/02/2021			3213.00
*****	17/07/2021	0.16	2.4	
*****	15/01/2022	0.07	1.2	3045.00

*****	16/07/2022	0.21	2.7	
*****	22/07/2022			2584.00
*****	21/01/2023	0.23	2.5	
*****	25/01/2023			1700.00
*****	08/07/2023	0.24	1.8	
*****	12/07/2023			1343.00
*****	29/12/2023			400.00
*****	04/04/2014	.83	8,00	
*****	11/02/2015	.6	7.2	514
*****	19/12/2016	1,00	9.3	
*****	28/01/2018	0.98	6.1	
*****	21/06/2019			374.00
*****	08/07/2021	0.03	0.3	
*****	01/10/2015	.05	.7	
*****	17/09/2017	0.09	0.6	
*****	05/11/2023	0.06	1.1	
*****	24/12/2016	0.16	1.8	
*****	30/12/2016			150
*****	28/02/2019			400.00
*****	26/11/2016	0.35	6.2	
*****	27/11/2016			603
*****	24/11/2017	0.31	6.9	
*****	26/11/2017			520
*****	12/12/2019	0.32	6.6	141.00
*****	26/03/2014	.13	1.8	
*****	03/06/2015	.18	4.2	995
*****	06/07/2013	.22	2.1	
*****	20/06/2015	.17	2.2	
*****	21/06/2015			163
*****	29/08/2018	0.42	6.5	
*****	14/06/2019	0.21	3.6	
*****	10/11/2019	0.22	3.4	
*****	14/11/2019			213.00
*****	22/02/2020	0.06	0.4	168.00
*****	19/09/2020	0.08	1.5	
*****	30/01/2021	0.20	3.2	
*****	13/03/2021	0.07	1.3	
*****	17/03/2021			221.00
*****	28/08/2021	0.10	1.9	
*****	01/09/2021			139.00
*****	09/01/2022	0.04	0.2	
*****	10/01/2022	0.05	0.3	
*****	11/01/2022	0.02	0.1	
*****	12/01/2022	0.01	0.02	
*****	12/02/2022	0.16	1.8	
*****	16/02/2022			148.00
*****	21/04/2022	0.16	2.8	
*****	16/07/2022	0.17	3.5	
*****	20/07/2022			153.00
*****	04/02/2023	0.23	2.4	

*****	08/02/2023			132.00
*****	28/05/2023	0.18	2.5	
*****	05/08/2023	0.15	3.0	
*****	10/08/2023			127.00
*****	20/03/2013	1.3	8.8	
*****	31/10/2013	.78	7.9	
*****	07/11/2015	.9	7.6	2018
*****	22/11/2017	0.36	3.9	1585
*****	30/01/2019	0.69	8.6	861.00
*****	18/02/2021			322.00
*****	09/07/2022	0.84	9.6	648.00
*****	13/06/2013	.04	.4	
*****	04/09/2013	.19	2.1	
*****	12/12/2013	.4	5.4	
*****	24/10/2014	.03	.3	
*****	11/12/2014	.11	1,00	
*****	13/12/2014			128
*****	12/03/2015	.43	5,00	
*****	06/09/2015			516
*****	07/05/2016	0.44	5.4	481
*****	14/02/2020	0.15	0.9	64.90
*****	12/01/2022	0.32	3.1	
*****	17/03/2022			78.90
*****	06/08/2023	0.02	0.1	
*****	21/09/2023	0.02	0.1	
*****	23/09/2023	0.06	0.4	
*****	26/09/2023	0.25	1.2	
*****	29/09/2023	0.24	2.0	
*****	04/10/2023	0.11	0.8	
*****	08/10/2023	0.05	0.3	
*****	10/10/2023	0.37	3.1	
*****	17/11/2023	0.33	1.8	
*****	18/11/2023	0.47	4.1	
*****	19/11/2023	0.49	4.2	
*****	22/11/2023	0.37	5.3	
*****	25/11/2023	0.38	6.4	
*****	14/02/2015	.56	9.6	
*****	09/04/2015	0,00	0,00	
*****	12/04/2015			86.2
*****	14/01/2016	.04	0.04	
*****	15/01/2016			78.5
*****	10/02/2017	0.02	0.2	
*****	12/02/2017			105
*****	06/04/2017			254
*****	30/08/2017	0.23	3.8	
*****	31/08/2017			383
*****	29/12/2017	0.06	0.6	
*****	30/12/2017			199
*****	28/02/2018	0.09	1.6	
*****	02/03/2018			250

*****	26/09/2018	0.13	1.7	195.00
*****	06/03/2019	0.21	3.5	169.00
*****	21/09/2019	0.21	2.9	
*****	25/09/2019			487.00
*****	07/03/2020	0.09	1.0	
*****	11/03/2020			261.00
*****	06/06/2020	0.15	1.8	
*****	10/06/2020			272.00
*****	19/12/2020	0.17	2.0	
*****	23/12/2020			271.00
*****	18/09/2021	0.12	1.7	
*****	22/09/2021			214.00
*****	16/03/2022			198.00
*****	30/07/2022	0.22	2.6	
*****	03/08/2022			189.00
*****	14/01/2023	0.20	2.9	
*****	15/01/2023			162.00
*****	24/06/2023	0.22	3.8	156.00
*****	09/12/2023	0.24	4.1	
*****	13/12/2023			180.00
*****	22/12/2013	.5	7.3	
*****	29/10/2016	0.45	6.2	706
*****	26/04/2013	.24	2.7	
*****	19/12/2013	.43	8.4	
*****	11/12/2013	.01	.1	
*****	15/09/2014	.84	9.3	
*****	01/11/2015	.2	1.3	
*****	06/11/2015			625
*****	26/11/2015	.1	.8	
*****	27/11/2015	.09	.7	
*****	03/12/2015	.32	3.4	
*****	06/12/2015	.44	4.8	
*****	02/01/2016	.58	5.1	
*****	16/10/2017	0.01	0,00	
*****	20/10/2017	0.16	1.3	
*****	25/10/2017	0.27	2.6	
*****	20/12/2017	0.48	5.6	
*****	23/12/2017			563
*****	31/01/2018	0.37	5.3	
*****	04/02/2018			585
*****	23/02/2018	0.45	6.2	
*****	24/02/2018			731
*****	11/08/2018	0.33	5.3	1692.00
*****	10/10/2018	0.03	0.2	
*****	12/10/2018			1510.00
*****	07/12/2018	0.14	1.8	
*****	07/02/2019			1299.00
*****	23/08/2019	0.44	5.0	
*****	24/08/2019			904.00
*****	20/02/2020	0.16	1.6	

*****	22/02/2020			773.00
*****	30/05/2015	.29	3.1	
*****	03/06/2015			540
*****	27/02/2016	0.6	5.1	
*****	28/02/2016			728
*****	09/10/2016	0.03	0.2	
*****	13/10/2016			1378
*****	26/03/2017	0.15	1.3	
*****	29/03/2017			1460
*****	15/10/2017	0.7	7.1	
*****	18/10/2017			1422
*****	08/04/2018	0.29	3.6	
*****	11/04/2018			1065
*****	16/09/2018	0.36	2.8	1302.00
*****	14/04/2019	0.03	0.3	1425.00
*****	12/05/2019	0.33	2.3	
*****	10/11/2019	0.53	5.1	
*****	14/11/2019			1640.00
*****	01/03/2020	0.41	4.5	
*****	04/03/2020			1281.00
*****	31/05/2020	0.14	1.0	
*****	06/06/2020			846.00
*****	30/08/2020	0.12	0.9	
*****	03/09/2020			365.00
*****	20/12/2020	0.12	1.1	
*****	24/12/2020			350.00
*****	17/01/2021	0.00	0.0	
*****	20/01/2021			353.00
*****	20/02/2021	0.00	0.0	
*****	21/02/2021			334.00
*****	13/06/2021	0.00	0.0	
*****	16/06/2021			308.00
*****	03/10/2021	0.00	0.0	
*****	06/10/2021			237.00
*****	23/01/2022	0.00	0.0	
*****	26/01/2022			248.00
*****	03/09/2022	0.00	0.0	
*****	04/09/2022			336.00
*****	24/12/2022	0.00	0.0	
*****	30/12/2022			335.00
*****	06/01/2023	0.00	0.0	
*****	11/01/2023			240.00
*****	21/01/2023	0.00	0.0	
*****	25/01/2023			231.00
*****	04/02/2023	0.03	0.3	
*****	08/02/2023			236.00
*****	18/03/2023	0.56	4.9	
*****	22/03/2023			261.00
*****	01/04/2023	0.30	2.0	
*****	05/04/2023			267.00

*****	22/04/2023	0.62	6.1	
*****	27/04/2023			225.00
*****	06/05/2023	0.36	3.8	
*****	10/05/2023			214.00
*****	26/05/2023	0.00	0.0	
*****	28/05/2023	0.12	1.0	
*****	31/05/2023			424.00
*****	07/06/2023	0.34	3.4	
*****	17/06/2023	1.15	13.7	
*****	18/06/2023			143.00
*****	15/07/2023	0.67	6.4	
*****	16/07/2023			214.00
*****	26/08/2023	0.10	0.7	
*****	27/08/2023			205.00
*****	09/12/2023	0.43	4.4	
*****	13/12/2023			139.00
*****	26/03/2014	.14	2.2	
*****	23/10/2015	.17	2.4	
*****	20/02/2016	0.15	2,00	
*****	16/04/2016	0.07	1,00	
*****	26/05/2016	0.1	1.3	
*****	25/08/2016	0.1	1.7	
*****	04/11/2016	0.09	1.6	
*****	22/02/2017	0.24	2.8	
*****	21/05/2017	0.15	2.5	
*****	18/06/2017	0.08	2.7	
*****	25/06/2017	0.1	2.4	
*****	02/07/2017	0.05	1.4	
*****	09/07/2017	0.02	0.6	
*****	15/07/2017	0.02	0.7	
*****	01/09/2017	0.17	3.4	
*****	15/10/2017	0.34	6,00	
*****	26/12/2017	0.17	2.5	
*****	31/12/2017	0.17	3.5	
*****	26/01/2018	0.09	2.1	
*****	25/02/2018	0.05	1.1	
*****	25/05/2018	0.17	4.0	
*****	20/10/2018	0.11	2.2	
*****	03/02/2019	0.04	0.4	
*****	01/05/2019	0.04	0.05	52.80
*****	05/05/2019	0.06	1.4	
*****	02/08/2019	0.05	1.0	
*****	03/08/2019			32.30
*****	29/08/2019	0.22	3.9	
*****	30/08/2019			130.00
*****	25/09/2019	0.10	2.2	
*****	26/09/2019			195.00
*****	25/10/2019	0.09	1.8	
*****	09/11/2019	0.05	0.8	
*****	14/11/2019	0.06	0.8	

*****	01/02/2020	0.04	0.6	
*****	07/05/2020	0.05	0.8	
*****	09/05/2020	0.07	1.5	257.00
*****	05/06/2020	0.05	1.0	227.00
*****	25/09/2020	0.04	0.7	
*****	16/12/2020	0.05	1.2	
*****	17/12/2020			162.00
*****	07/01/2021	0.06	0.9	
*****	02/04/2021	0.03	0.5	
*****	08/05/2021	0.09	1.2	
*****	14/08/2021	0.06	1.1	
*****	04/09/2021	0.08	1.3	
*****	11/09/2021	0.07	1.0	
*****	12/09/2021			140.00
*****	23/09/2021	0.10	1.3	
*****	11/12/2021			118.00
*****	16/12/2021	0.09	1.6	
*****	24/12/2021	0.06	0.7	
*****	26/12/2021	0.06	1.0	
*****	29/12/2021	0.10	2.4	
*****	17/03/2022	0.09	1.7	
*****	21/05/2022	0.09	1.6	
*****	26/05/2022	0.09	1.8	216.00
*****	03/09/2022	0.16	2.7	
*****	08/11/2022	0.10	1.6	
*****	19/11/2022	0.18	2.9	
*****	23/11/2022			203.00
*****	21/01/2023	0.11	2.2	
*****	25/01/2023			353.00
*****	21/04/2023	0.13	2.1	
*****	23/06/2023	0.09	2.0	
*****	08/07/2023	0.11	2.0	
*****	13/07/2023			228.00
*****	08/08/2023	0.13	1.9	
*****	31/08/2023	0.11	1.6	
*****	16/12/2015	.22	2.8	
*****	02/01/2016	0.16	3.5	
*****	06/01/2016			104
*****	27/02/2016	0.16	6.6	
*****	28/02/2016			63.8
*****	31/03/2016	0.14	3.8	
*****	06/07/2016	0.19	4.9	
*****	24/08/2016	0.12	0.8	
*****	02/09/2016	0.21	5.3	
*****	24/09/2016	0.25	3.8	
*****	13/10/2016	0.2	4.4	
*****	21/10/2016	0.22	5.7	423
*****	18/11/2016	0.11	3.5	
*****	18/12/2016	0.08	1.5	
*****	07/01/2017	0.23	6.3	

*****	28/04/2017	0.27	0.32	
*****	29/04/2017			580
*****	01/07/2017	0.14	3.5	
*****	28/09/2017	0.16	2.7	
*****	01/10/2017			459
*****	07/12/2017	0.01	0.1	
*****	27/04/2018	0.1	1.6	
*****	28/04/2018			339
*****	25/05/2018	0.12	2.3	
*****	19/08/2018	0.08	1.5	
*****	27/10/2018	0.09	1.3	349.00
*****	23/01/2019	0.11	1.9	
*****	02/02/2019			420.00
*****	25/05/2019	0.06	1.4	
*****	13/11/2019	0.12	1.6	
*****	21/06/2020	0.07	1.3	
*****	06/11/2020	0.11	2.0	
*****	12/09/2021	0.02	0.5	
*****	18/12/2021	0.11	3.6	
*****	23/04/2016	0.15	1.8	147
*****	18/12/2014	1.04	16.6	1988
*****	09/05/2015			1305
*****	17/10/2015	1.67	21.9	
*****	22/10/2015			1490
*****	09/04/2016	1.08	12.1	
*****	10/04/2016			1662
*****	08/10/2016	1.04	16.8	
*****	13/10/2016			1037
*****	29/03/2017	1.31	18.3	1521
*****	18/10/2017			1627
*****	15/04/2018	0.77	12.3	
*****	20/04/2018			1621
*****	22/12/2018	0.77	13.7	1767.00
*****	14/03/2013	.12	1.7	
*****	31/08/2017	0.21	2.9	
*****	01/09/2017			703
*****	24/07/2018	0.10	1.0	
*****	03/10/2018	0.16	1.3	
*****	10/11/2018	0.12	1.1	
*****	29/05/2019	0.31	4.0	443.00
*****	26/07/2019	0.33	4.4	507.00
*****	08/08/2019	0.18	2.7	1108.00
*****	06/09/2019	0.19	2.6	1724.00
*****	18/01/2020	0.10	1.6	1742.00
*****	19/09/2020	0.19	3.5	
*****	20/09/2020			1944.00
*****	16/12/2020			1911.00
*****	13/02/2021	0.08	0.9	
*****	05/03/2021	0.14	2.5	
*****	06/03/2021			1863.00

*****	28/04/2021	0.08	0.8	
*****	23/10/2021	0.12	1.7	
*****	27/10/2021			1524.00
*****	25/12/2021	0.03	0.4	
*****	30/04/2022	0.12	1.8	
*****	04/05/2022			1480.00
*****	10/09/2022	0.13	2.1	
*****	11/09/2022			878.00
*****	25/02/2023	0.16	2.4	
*****	26/02/2023			492.00
*****	20/05/2023	0.22	3.9	
*****	24/05/2023			614.00
*****	04/11/2023	0.13	2.0	
*****	05/11/2023			1446.00
*****	19/12/2014			4561
*****	17/06/2015			3939
*****	10/09/2015			3729
*****	20/03/2016	0.79	15.2	2417
*****	27/11/2016	0.67	10.8	
*****	30/11/2016			2392
*****	28/05/2017	0.65	10.5	
*****	01/06/2017			2501
*****	14/07/2016	0.14	2.9	1445
*****	17/04/2015	.39	4.9	
*****	19/04/2015			451
*****	20/10/2018	0.16	2.2	862.00
*****	13/04/2019	0.13	1.6	1144.00
*****	19/10/2019	0.20	3.1	
*****	24/10/2019			848.00
*****	23/05/2020	0.21	2.9	
*****	27/05/2020			653.00
*****	16/01/2021	0.19	2.4	
*****	20/01/2021			867.00
*****	08/05/2021	0.23	3.0	
*****	13/05/2021			841.00
*****	30/10/2021	0.34	3.7	
*****	04/11/2021			409.00
*****	18/06/2022	0.19	3.3	
*****	22/06/2022			1096.00
*****	28/01/2023	0.14	2.2	
*****	01/02/2023			1155.00
*****	10/06/2016	0.21	2.5	169
*****	29/10/2016	0.19	1.5	
*****	26/02/2018	0,00	0,00	
*****	10/02/2019	0.15	1.5	111.00
*****	11/07/2019	0.18	1.2	
*****	13/07/2019			129.00
*****	29/09/2019	0.18	1.4	
*****	02/10/2019			82.50
*****	30/10/2019	0.13	1.3	349.00

*****	28/11/2019	0.15	1.3	
*****	29/11/2019			403.00
*****	12/06/2020	0.18	1.8	317.00
*****	22/11/2020	0.17	1.6	
*****	25/11/2020			317.00
*****	09/05/2021	0.22	1.5	
*****	14/05/2021			233.00
*****	04/09/2021	0.15	1.0	336.00
*****	23/01/2022	0.17	1.2	
*****	16/03/2022			220.00
*****	03/09/2022	0.18	1.5	
*****	08/09/2022			575.00
*****	19/02/2023	0.15	1.1	
*****	23/02/2023			319.00
*****	06/08/2023	0.24	1.8	
*****	10/08/2023			207.00
*****	04/12/2016	0.57	10.4	2036
*****	12/07/2017	0.32	3.7	450
*****	11/08/2017	0.07	0.5	
*****	23/02/2018	0.47	8.1	
*****	28/02/2018			1519
*****	01/06/2018	0.41	5.2	5000.00
*****	25/08/2018	0.41	5.8	3308.00