SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Onureg 300 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg azacitidine.

Excipient with known effect
Each film-coated tablet contains 5.42 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Brown, oval, film-coated tablet, 19.0x9.0 mm, debossed with “300” on one side and “ONU” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Onureg is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

4.2 Posology and method of administration

Onureg treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products.

Patients are to be treated with an anti-emetic 30 minutes prior to each dose of Onureg for the first 2 treatment cycles. Anti-emetic prophylaxis may be

omitted after 2 cycles, if there has been no nausea and vomiting (see section 4.4).

Posology
The recommended dose is 300 mg azacitidine orally once daily. Each repeated cycle consists of a treatment period of 14 days followed by a treatment free period of 14 days (28-day treatment cycle).

Onureg treatment should be continued until no more than 15% blasts are observed in peripheral blood or bone marrow or until unacceptable toxicity (see dose schedule modification guidance for disease relapse).

Onureg should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment. Healthcare professionals are recommended to verify the name of the medicinal product, dose and administration route.

Laboratory tests
Complete blood counts should be performed prior to initiation of therapy. Complete blood count monitoring is also recommended every other week for the first 2 cycles (56 days), every other week for the next 2 cycles after dose adjustment, and monthly thereafter, prior to the start of subsequent cycles of treatment (see section 4.4).

Dose schedule modification for AML disease relapse
In the case of disease relapse, with 5% to 15% blasts in peripheral blood or bone marrow, in conjunction with a clinical assessment, an extension of the dosing schedule from 14 to 21 days of repeated 28-day cycles should be considered. Dosing should not exceed 21 days during any 28-day period. Onureg should be discontinued if more than 15% blasts are observed in either the peripheral blood or bone marrow or at the physician's discretion.

Dose adjustment for adverse reactions
Dose modification guidelines for haematologic and non-haematologic adverse reactions are recommended based on clinical and laboratory findings (see Table 1).

Table 1: Dose adjustments for haematologic and non-haematologic adverse reactions

Criteria*	**Recommended action**
Grade 4 neutropenia or Grade 3 neutropenia with fever	First occurrence • Interrupt Onureg. Resume the treatment cycle at the same dose once neutrophils return to Grade 2 or lower. • Use supportive care such as granulocyte colony stimulating factor (GCSF), as clinically indicated (see section 4.4). Occurrence in 2 consecutive cycles • Interrupt Onureg. Resume the treatment cycle at a reduced dose of 200 mg after neutrophils return to Grade 2 or lower. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Onureg.

Criteria*	Recommended action
	• Use supportive care such as GCSF, as clinically indicated (see section 4.4).
Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding	First occurrence • Interrupt Onureg. Resume the treatment cycle at the same dose once platelets return to Grade 2 or lower. Occurrence in 2 consecutive cycles • Interrupt Onureg. Resume the treatment cycle at a reduced dose of 200 mg after platelets return to Grade 2 or lower. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Onureg.
Grade 3 or higher nausea, vomiting or diarrhoea	• Interrupt Onureg. Resume the treatment cycle at the same dose once toxicity has resolved to Grade 1 or lower. • Use supportive care such as anti-emetic therapy and treat diarrhoea at the onset of symptoms (see section 4.4). • If event re-occurs, interrupt dose until resolved to Grade 1 or lower and reduce the dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Onureg.
Other Grade 3 or higher non-haematological events	• Interrupt Onureg and provide medical support according to local recommendations. Resume the treatment cycle at the same dose once toxicity has resolved to Grade 1 or lower. • If the toxicity re-occurs, interrupt Onureg until resolved to Grade 1 or lower and reduce dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Onureg.

* Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening. Toxicity grades
are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.3 (NCI-CTCAE v4.3).

Missed or delayed doses
If a dose of Onureg is missed, or not taken at the usual time, the dose should be taken as soon as possible on the same day. Then, the next scheduled dose should be taken at the normal time the following day. Two doses should not be taken on the same day.

If a dose is vomited, another dose must not be taken on the same day. Instead return to the normal time of dose administration the following day.

Special populations

Elderly patients
No dose adjustments are recommended for patients over 65 years of age (see section 5.2).

Renal impairment
Onureg can be administered to patients with mild, moderate or severe renal impairment without initial dose adjustment (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (BIL) ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or BIL 1 to 1.5 × ULN and any AST) (see section 5.2).

Patients with moderate (BIL > 1.5 to 3 × ULN) and severe hepatic impairment (BIL > 3 × ULN) should be monitored more frequently for adverse reactions and appropriate dose adjustment should be made (see Table 1).

Paediatric population
The safety and efficacy of Onureg in children and adolescents below 18 years have not been established. No data are available.

Method of administration
Onureg is for oral use.

Onureg can be taken with or without food. The tablets should be swallowed whole with a glass of water at about the same time each day. They should not be split, crushed, dissolved or chewed (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity
Treatment with Onureg can be associated with neutropenia, thrombocytopenia and febrile neutropenia (see section 4.8 for frequencies). Interruption, reduction or discontinuation of Onureg may be necessary to manage haematological toxicities. Patients should be advised to promptly report febrile episodes. Patients with low platelet counts should be advised to report early signs or symptoms of bleeding. Supportive care such as antibiotics and/or antipyretics for management of infection/fever and GCSF for neutropenia should be provided based on individual patient characteristics, treatment response and according to the current clinical guidelines (see section 4.2 Table 1).
Differentiation syndrome
Cases of differentiation syndrome (also known as retinoic acid syndrome)

have been reported in patients receiving oral azacitidine. Differentiation syndrome may be fatal and symptoms and clinical findings include respiratory distress, pulmonary infiltrates, fever, rash, pulmonary oedema, peripheral oedema, rapid weight gain, pleural effusions, pericardial effusions, hypotension and renal dysfunction (see section 4.8). Treatment with high-dose IV corticosteroids and haemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation of oral azacitidine should be considered until resolution of symptoms and if resumed, caution is advised.

Gastrointestinal toxicity

Gastrointestinal toxicities were the most frequent adverse reactions in patients treated with Onureg (see section 4.8). Patients should be administered prophylactic anti-emetic therapy for the first 2 cycles of Onureg treatment (see section 4.2). Diarrhoea should be treated promptly at the onset of symptoms. Interruption, reduction or discontinuation of Onureg may be necessary to manage gastrointestinal toxicities (see section 4.2).

Women of childbearing potential/Contraception in males and females

Women of childbearing potential have to use effective contraception during and up to 6 months after treatment. Men have to use effective contraception during and up to 3 months after treatment (see section 4.6).

Lactose intolerance

Onureg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical drug-drug interaction studies with azacitidine have been conducted.

In case of concomitant administration with other antineoplastic agents, caution and monitoring is recommended as an antagonistic, additive, or synergistic pharmacodynamic effect cannot be excluded. These effects may be dependent on the dose, sequence and schedule of administration.

Onureg exposure was minimally affected when co-administered with a proton pump inhibitor (omeprazole). Therefore, dose modification is not required when Onureg is co-administered with proton pump inhibitors or other pH modifiers.

An *in vitro* study of azacitidine with human liver fractions indicated that azacitidine was not metabolised by cytochrome P450 isoforms (CYPs). Therefore, interactions with CYP inducers or inhibitors are considered unlikely (see section 5.2).

Clinically relevant inhibitory or inductive effects of azacitidine on the metabolism of cytochrome P450 substrates are unlikely (see section 5.2). No clinically relevant

drug-drug interactions are expected when Onureg is co-administered with substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3, or organic cation transporter (OCT) OCT2.

Azacitidine is not a substrate of P-gp, therefore it is not expected to interact with P-gp inducers or inhibitors.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential have to use effective contraception during and up to 6 months after treatment. Men should be advised not to father a child while receiving treatment and have to use effective contraception during and up to 3 months after treatment (see sections 4.4 and 5.3).

Pregnancy

There are no adequate data from the use of Onureg in pregnant women. Studies in mice and rats have shown reproductive and developmental toxicity (see section 5.3). The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, Onureg is not recommended during pregnancy (especially during the first trimester, unless clearly necessary) and in women of childbearing potential not using contraception. The advantages of treatment should be weighed against the possible risk for the foetus in every individual case. If a patient or partner becomes pregnant while taking Onureg, the patient should be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether azacitidine or its metabolites are excreted in human milk. Due to the potential serious adverse reactions in the breastfed child, breast-feeding is contraindicated during Onureg therapy (see section 4.3).

Fertility

There are no human data on the effect of azacitidine on fertility. In animals, adverse effects of azacitidine on male fertility have been documented (see section 5.3). Patients who wish to conceive a child should be advised to seek reproductive counselling and cryo-conservation of either the ovum or sperm prior to starting Onureg treatment.

4.7 Effects on ability to drive and use machines

Onureg has minor influence on the ability to drive and use machines. Fatigue has been reported with the use of Onureg. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are nausea (64.8%), vomiting (59.7%), diarrhoea (50.4%), neutropenia (44.5%), fatigue/asthenia (44.1%)[5], constipation (38.6%), thrombocytopenia (33.5%), abdominal pain (21.6%)[4], respiratory tract infection (17%)[2], arthralgia (13.6%), decreased appetite (12.7%), febrile neutropenia (11.9%), back pain (11.9%), leucopenia (10.6%), pain in extremity (10.6%) and pneumonia (10.2%)[1].

Serious adverse reactions occurred in 16.1% of patients receiving Onureg. The most common serious adverse reactions are febrile neutropenia (6.8%) and pneumonia (5.1%)[1].

Permanent discontinuation of Onureg due to an adverse reaction occurred in 6.8% of patients. The most common adverse reactions requiring permanent discontinuation are nausea (2.1%), diarrhoea (1.7%), and vomiting (1.3%).

Dose interruptions due to an adverse reaction occurred in 36.4% of patients who received Onureg. Adverse reactions requiring dose interruption include neutropenia (19.9%), thrombocytopenia (8.5%), nausea (5.5%), diarrhoea (4.2%), vomiting (3.8%), pneumonia (3.4%)[1], leucopenia (2.5%), febrile neutropenia (2.1%), and abdominal pain (2.1%)[4].

Dose reductions due to an adverse reaction period occurred in 14% of patients who received Onureg. Adverse reactions requiring dose reduction included neutropenia (5.5%), diarrhoea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%).

Tabulated list of adverse reactions

Table 2 presents the frequency category of ADRs reported during clinical trials with Onureg and post-marketing use. A total of 236 patients received Onureg in the pivotal Phase 3 study. The median treatment duration was 11.6 months (range: 0.5 to 74.3 months) in the Onureg arm.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse reactions are presented in the table below according to the highest frequency observed.

Table 2: Adverse drug reactions (ADRs) in AML patients receiving Onureg maintenance therapy

System organ class	All grades[a] frequency
Infections and infestations	**Very common** Pneumonia[1, 6], respiratory tract infection[2] **Common** Influenza, urinary tract infection[3], bronchitis, rhinitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**Not known** Differentiation syndrome
Blood and lymphatic system disorders	**Very common** Neutropenia, thrombocytopenia[6], febrile neutropenia[6], leucopenia
Metabolism and nutrition disorders	**Very common** Decreased appetite
Psychiatric disorders	**Common** Anxiety
Gastrointestinal disorders	**Very common** Nausea, vomiting, diarrhoea, constipation, abdominal pain[4]
Musculoskeletal and connective tissue disorders	**Very common** Arthralgia, back pain, pain in extremity
General disorders and administration site conditions	**Very common** Fatigue / asthenia[5]
Investigations	**Common** Weight decreased

[a] All AEs with at least 5.0% of patients in the Onureg arm and at least 2.0% higher frequency than the placebo arm.
[1] Grouped terms include pneumonia, bronchopulmonary aspergillosis, lung infection, Pneumocystis jirovecii pneumonia, atypical pneumonia, pneumonia bacterial, and pneumonia fungal.
[2] Grouped terms include upper respiratory tract infection, respiratory tract infection, and respiratory tract infection viral.
[3] Grouped terms include urinary tract infection, urinary tract infection bacterial, Escherichia urinary tract infection, and cystitis.
[4] Grouped terms include abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain.
[5] Grouped terms include fatigue and asthenia.
[6] Adverse reactions in which at least one was considered to be life threatening (if the outcome of the reaction was death, it is included with death cases).

Description of selected adverse reactions

Haematological toxicity

New or worsening Grade 3 or higher neutropenia (41.1%), thrombocytopenia (22.5%), or febrile neutropenia (11.4%) were commonly reported adverse reactions in patients treated with Onureg. The first occurrence of Grade 3 or 4 neutropenia, thrombocytopenia, or febrile neutropenia occurred within the first 2 cycles in 19.9%, 10.6%, and 1.7%, respectively in patients treated with Onureg. See section 4.2 for monitoring and management guidance.

Gastrointestinal toxicity
Gastrointestinal toxicities were the most frequent adverse reactions in patients treated with Onureg. Nausea (64.8%), vomiting (59.7%), and diarrhoea (50.4%) were reported in patients treated with Onureg. Grade 3 or higher diarrhoea occurred in 5.1% of patients and Grade 3 or higher vomiting and nausea occurred in 3.0% and 2.5%, respectively in patients treated with Onureg. The first occurrence of Grade 3 or 4 nausea, vomiting, or diarrhoea occurred within the first 2 cycles in 1.7%, 3.0%, and 1.3%, respectively, in patients treated with Onureg. See section 4.2 for monitoring and management guidance.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdose, the patient should be monitored with appropriate blood counts and supportive treatment should be provided, as necessary, according to local recommendations. There is no known specific antidote for an overdose with Onureg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues, ATC code: L01BC07

Mechanism of action
Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. Incorporation of azacitidine into the DNA of AML cells, modified epigenetic pathways through the inhibition of DNA methyltransferases, and reduction of DNA methylation. This led to alteration of gene expression, including re-expression of genes regulating tumour suppression, immune pathways, cell cycle, and cell differentiation. Incorporation of azacitidine into the RNA of AML cells, inhibited RNA methyltransferase, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis.

Clinical efficacy and safety
The efficacy and safety of Onureg was studied in a multi-centre, placebo-controlled, Phase 3 study QUAZAR AML-001 (CC-486-AML-001) with a

double-blind, randomised, parallel-group design which evaluated Onureg versus placebo as maintenance therapy in AML patients. Patients were enrolled with *de novo* AML, AML secondary to prior diagnosis of myelodysplastic syndromes (MDS), or chronic myelomonocytic leukaemia (CMML); the patients were aged ≥ 55 years, and had achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) within 4 months (+/- 7 days) after intensive induction chemotherapy with or without consolidation therapy. Patients were not eligible for HSCT at the time of randomisation, which included patients who did not have a transplant donor, or who chose not to proceed to HSCT.

Patients in both treatment arms received best supportive care as deemed necessary by the investigator. Best supportive care included, but was not limited to, treatment with red blood cell (RBC) transfusions, platelet transfusions, use of erythropoiesis stimulating agent, antibiotic, antiviral and/or antifungal therapy, GCSF, anti-emetic therapy, and nutritional support.

Patients who achieved a CR/CRi after completion of intensive induction therapy with or without consolidation were administered Onureg 300 mg (N=236) or placebo (N=233) once daily on Days 1 through 14 of each 28-day cycle. In the event of disease relapse (5% to 15% blasts in peripheral blood or bone marrow), the dose schedule was extended to 21 days of repeated 28-day treatment cycles per medical discretion. Treatment continued until disease progression (more than 15% blasts were observed in peripheral blood or bone marrow) or until unacceptable toxicity.

A total of 472 patients were randomised 1:1 between Onureg and placebo treatment arms. Baseline demographic and disease characteristics for the AML patient population were balanced between treatment arms as shown in Table 3. The median treatment duration was 11.6 months (range: 0.5 to 74.3 months) for the Onureg arm *versus* 5.7 months (range: 0.7 to 68.5 months) for the placebo arm. A total of 51 patients (21%) receiving Onureg and 40 patients (17%) receiving placebo extended their dose schedule to 300 mg daily for 21 days due to AML disease relapse.

Of the 469 patients in the Phase 3 study who received treatment, 61% (285/469) were 65 years of age or older and 11% (51/469) were 75 years of age or older. No overall differences in safety or efficacy of Onureg were observed between these patients and younger patients.

Table 3: Baseline demographics and disease-related characteristics in study CC-486-AML-001

Parameter	**Onureg (N = 238)**	**Placebo (N = 234)**
Age (years)		
Median (min, max)	68.0 (55, 86)	68.0 (55, 82)
Age category, n (%)		
<65 years	66 (27.7)	68 (29.1)
≥65 years to <75 years	144 (60.5)	142 (60.7)
≥75 years	28 (11.8)	24 (10.3)
Sex, n (%)		
Male	118 (49.6)	127 (54.3)
Female	120 (50.4)	107 (45.7)
Race, n (%)		

Parameter	Onureg (N = 238)	Placebo (N = 234)
White	216 (90.8)	197 (84.2)
Black or African American	2 (0.8)	6 (2.6)
Asian	6 (2.5)	20 (8.5)
Other	12 (5.0)	11 (4.7)
Not collected or reported	2 (0.8)	0 (0)
ECOG performance status, n (%)		
0	116 (48.7)	111 (47.4)
1	101 (42.4)	106 (45.3)
2	21 (8.8)	15 (6.4)
3	0 (0)	2 (0.9)
Cytogenetic risk status at diagnosis, n (%)		
Intermediate risk[1]	203 (85.3)	203 (86.6)
Poor risk[2]	35 (14.7)	31 (13.2)
Initial AML classification, n (%)		
AML with recurrent genetic abnormalities	39 (16.4)	46 (19.7)
AML with myelodysplasia-related changes	49 (20.6)	42 (17.9)
Therapy related myeloid neoplasms	2 (0.8)	0 (0)
AML not otherwise specified	148 (62.2)	145 (62.0)
Missing	0 (0)	1 (0.4)
Type of AML, n (%)		
Primary (de novo)	213 (89.5)	216 (92.3)
Secondary	25 (10.5)	18 (7.7)
MRD status at randomisation[3], n (%)		
Negative	133 (55.9)	111 (47.4)
Positive	103 (43.3)	116 (49.6)
Missing	2 (0.8)	7 (3.0)

AML=Acute myelogenous leukemia; MDS=Myelodysplastic syndrome; CMML=Chronic myelomonocytic Leukemia; ECOG=Eastern cooperative oncology group; CR=Morphologic complete remission; CRi=Morphologic CR with incomplete blood count recovery.
[1] Intermediate risk was defined as normal cytogenetics +8, t(9;11), or other undefined.
[2] Poor risk was defined as complex (≥ 3 abnormalities): -5; 5q-; -7; 7q-; 11q23 - non t(9;11); inv(3); t(3;3); t(6;9); or t(9;22). Source for Intermediate and Poor Risk: National comprehensive cancer network clinical practice guidelines in oncology for AML.
[3]MRD status in bone marrow was measured during screening period by flow cytometric assay at a sensitivity level of 0.1%.

Most patients received consolidation therapy after induction therapy in both the Onureg (78%) and placebo (82%) treatment arms; more than 90% of these patients in each treatment arm received 1 or 2 cycles of consolidation therapy after induction therapy (Table 4).

Table 4: Consolidation therapy in study CC-486-AML-001

Parameter	Onureg (N=238)	Placebo (N=234)
Received consolidation therapy following induction		
Yes, n (%)	186 (78.2)	192 (82.1)
1 Cycle, n (%)	110 (46.2)	102 (43.6)
2 Cycles, n (%)	70 (29.4)	77 (32.9)
3 Cycles, n (%)	6 (2.5)	13 (5.6)
No, n (%)	52 (21.8)	42 (17.9)
CR / CRi status at randomisation		
CR, n (%)	183 (76.9)	177 (75.6)
CRi, n (%)	50 (21.0)	44 (18.8)
Not in CR/CRi [a], n (%)	5 (2.1)	11 (4.7)
Missing, n (%)	0 (0)	2 (0.9)

CR=Complete remission; CRi=Morphologic CR with incomplete blood count recovery.
[a] These patients had baseline bone marrow of less than 5% blasts and both ANC $<1 \times 10^9$ and platelets $<100 \times 10^9$.

The efficacy of Onureg in adult patients with AML was established based on overall survival (OS) and relapse-free survival (RFS).

The efficacy results are summarised in the Table 5.

Table 5: CC-486-AML-001 efficacy results (ITT Population)

Endpoints	Onureg (N=238)	Placebo (N=234)
Overall survival		
OS events, n (%)	158 (66.4)	171 (73.1)
Median OS, months (95% CI)	24.7 (18.7, 30.5)	14.8 (11.7, 17.6)
Hazard ratio (95% CI) p-value	0.69 (0.55, 0.86) 0.0009	
Relapse-free survival		
Events, n (%)	164 (68.9)	181 (77.4)
Median RFS, months (95% CI)	10.2 (7.9, 12.9)	4.8 (4.6, 6.4)
Hazard ratio (95% CI) p-value	0.65 (0.52, 0.81) 0.0001	
Time to relapse		
Relapsed, n (%)	154 (64.7)	179 (76.5)
Median time to relapse, months (95% CI)	10.2 (8.3, 13.4)	4.9 (4.6, 6.4)
Time to discontinuation from treatment		
Treatment discontinued, n (%)	193 (81.1)	208 (88.9)
Median time to treatment discontinuation, months (95% CI)	11.4 (9.8, 13.6)	6.1 (5.1, 7.4)
Treatment discontinued – disease relapse, n (%)	143 (60.1)	180 (76.9)

CI=Confidence interval.

Prespecified subgroup analyses of OS and RFS showed a consistent treatment effect for Onureg across demographic and disease-related subgroups including baseline cytogenetic risk, the number of prior consolidation cycles received, and CR/CRi status.

The Kaplan-Meier curves display the OS (see Figure 1) and RFS (see Figure 2) results.

Figure 1: Kaplan-Meier curve for overall survival: Onureg *versus* placebo (ITT Population)

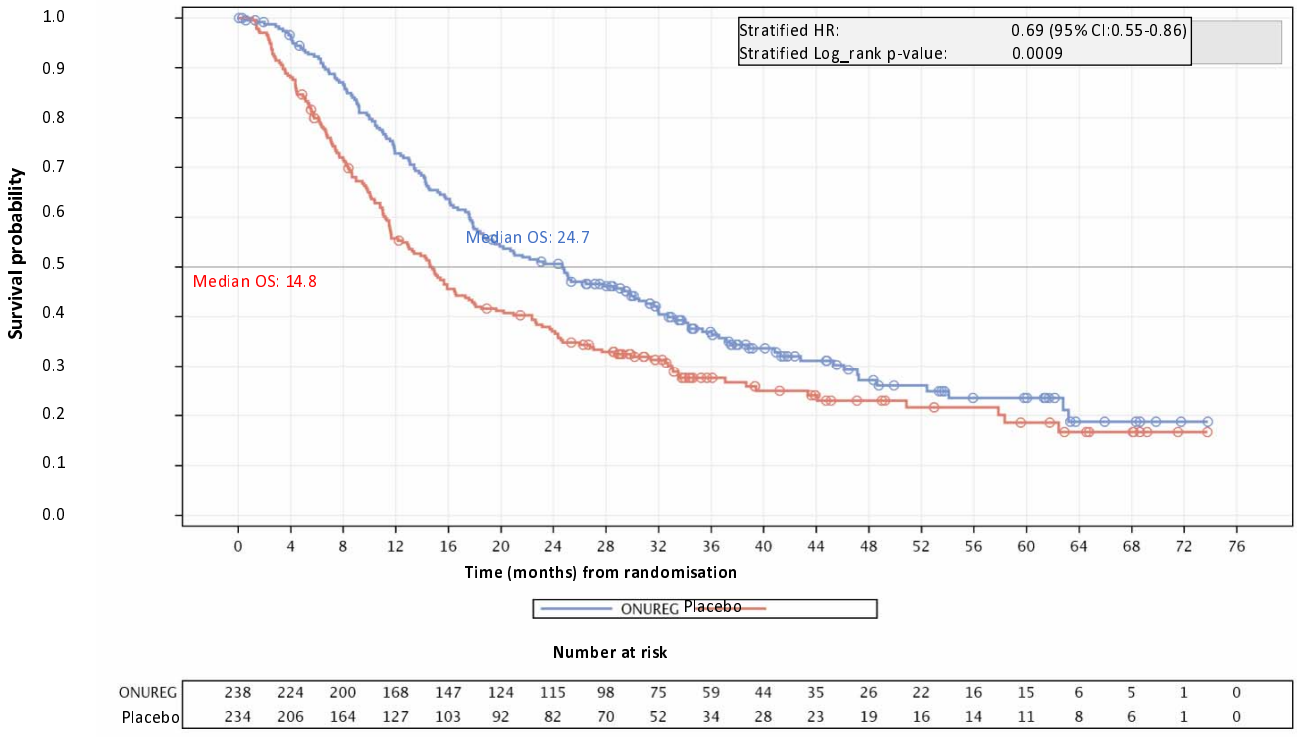
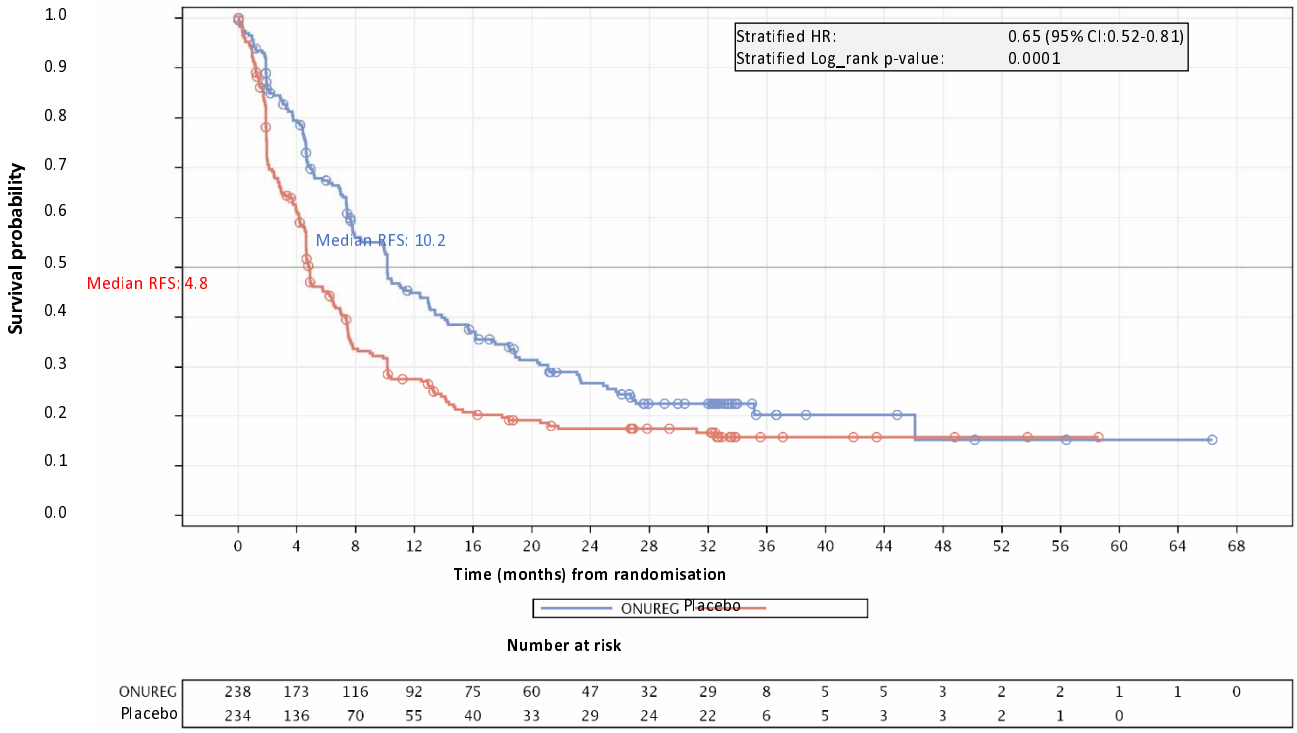


Figure 2: Kaplan-Meier curve for relapse free survival: Onureg *versus* placebo (ITT Population)



In patients who had their dose schedule extended to 300 mg for 21 days due to disease relapse, the median OS (22.8 months for Onureg and 14.6 months for placebo) and median RFS (7.4 months for Onureg and 4.6 months for placebo) were comparable to the overall study results.

Onureg demonstrated a favorable treatment effect for OS compared with placebo in both minimal residual disease (MRD)-positive and MRD-negative patients. The treatment effect for OS was more pronounced in MRD-positive patients (HR=0.69; 95% CI: 0.51, 0.93) than in MRD-negative patients (HR=0.81; 95% CI: 0.59, 1.12).

Health related quality of life (HRQoL)
HRQoL was assessed using the Functional assessment of chronic illness therapy-fatigue scale (FACIT – fatigue scale) and the Five dimensions three levels (EQ-5D-3L) health utility index and visual analogue scale (VAS). At baseline, patients had a low level of fatigue and good level of HRQoL that were generally comparable to those of the general population of similar age. This level of HRQoL was maintained over time with Onureg, as compared to baseline, as well as to placebo. Both the time to definitive deterioration and the proportion of patients experiencing clinically meaningful deterioration was found to be similar between those receiving Onureg and placebo. Overall, the findings demonstrate that HRQoL was similar between Onureg treatment and placebo arms, with no clinically meaningful deterioration over time.

5.2 Pharmacokinetic properties

Absorption

Exposure was generally linear with dose-proportional increases in systemic exposure; high intersubject variability was observed. The geometric mean (coefficient of variation [%CV]) C_{max} and AUC values after oral administration of a 300 mg single dose were 145.1 ng/mL (63.7) and 241.6 ng h/mL (64.5), respectively. Multiple dosing at the recommended dose regimen did not result in drug accumulation. Absorption of azacitidine was rapid, with a median T_{max} of 1 hour post dose. Mean oral bioavailability relative to subcutaneous (SC) administration was approximately 11%.

Effect of food

The impact of food on the exposure of Onureg was minimal. Therefore, Onureg can be administered with or without food.

Distribution

After oral administration, the geometric mean apparent volume of distribution was 12.6 L/kg for a 70 kg person. The plasma protein binding of azacitidine was 6 to 12%.

Biotransformation

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs). Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase.

Elimination

The geometric mean apparent clearance was 1242 L/hour and the geometric mean half-life was approximately 0.5 hours. Following intravenous administration of ^{14}C azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Faecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following subcutaneous administration of ^{14}C-azacitidine was 50%. The amount of unchanged azacitidine recovered in urine relative to dose was < 2% following either subcutaneous (SC) or oral administration. Faecal excretion has not been measured following oral administration.

Pharmacodynamic effects

The epigenetic regulatory effect of azacitidine on DNA global methylation reduction in the blood was sustained with prolonged exposure of 300 mg daily administered for 14 or 21 days of a 28-day cycle in myeloid cancers including AML patients from a Phase 1/2 study. A positive correlation was observed between azacitidine plasma exposure and the pharmacodynamic effect of reduction in global DNA methylation in blood.

Special populations

Elderly

In a population pharmacokinetics (PK) analysis from 286 AML patients, age (46 to 93 years) did not have clinically meaningful effects on the PK of Onureg. Therefore, dose modification for Onureg is not required, regardless of patient age.

Hepatic impairment
No formal studies have been conducted in patients with hepatic impairment. Hepatic impairment is unlikely to affect the PK to a clinically relevant extent since azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. A population PK analysis determined that AST (8 to 155 U/L), ALT (5 to 185 U/L) and mild hepatic impairment (BIL ≤ ULN and AST > ULN, or BIL 1 to 1.5 × ULN and any AST) did not have clinically meaningful effects on the PK of azacitidine. The effects of moderate to severe hepatic impairment (BIL > 1.5 × ULN and any AST) on the PK of azacitidine is unknown.

Renal impairment
In patients with cancer, the PK of azacitidine in 6 patients with normal renal function (CLcr >80 mL/min) and 6 patients with severe renal impairment (CLcr <30 mL/min) were compared following daily subcutaneous dosing (Days 1 through 5) at 75 mg/m^2/day. Severe renal impairment increased azacitidine exposure by approximately 70% after single and 41% after multiple subcutaneous administrations. This increase in exposure was not correlated with an increase in adverse events.

A population PK analysis following a 300 mg dose of Onureg determined that patients with mild (CLcr: ≥ 60 to < 90 mL/min), moderate (CLcr: ≥30 to <60 mL/min), and severe (CLcr: <30 mL/min) renal impairment had 19%, 25%, and 38% increases in azacitidine plasma AUC, respectively. The effect of severe renal impairment on Onureg was similar to the above referenced clinical renal impairment study with injectable azacitidine (~40% increase in AUC). The exposure of azacitidine (AUC) is approximately 75% lower after oral administration relative to the exposure achieved following SC administration; therefore, an increase in exposure of approximately 40% following oral administration is still considered safe and tolerable. Thus, no dose adjustment of Onureg is recommended in patients with mild, moderate, or severe renal impairment.

Race/ethnicity
The effects of race/ethnicity on the PK of Onureg is unknown.

5.3 Preclinical safety data

In a 14-day oral toxicity study in dogs, mortality occurred at doses of 8 and 16 mg/m^2/day. The maximum tolerated dose (MTD) was 4 mg/m^2/day. At 1 or all doses, pancytopenia correlated with bone marrow hypoplasia, lymphoid depletion, gland/lumen dilation and single cell necrosis in mucosal crypts of small and large intestines and/or centrilobular hepatocellular vacuolation were observed. At the MTD, these findings were partially or completely resolved after 3 weeks. Following parenteral azacitidine administrations at comparable dose ranges, mortality and similar target organ toxicities were observed in rodents, dogs and monkeys. Non-clinical data from repeat-dose toxicity studies with azacitidine revealed no special hazard for humans.

Azacitidine induces both gene mutations and chromosomal aberrations in bacterial and mammalian cell systems *in vitro*. The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumours of the haematopoietic system in female mice, when administered intraperitoneally 3 times per week for 52 weeks. An increased incidence of tumours in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine administered

intraperitoneally for 50 weeks. A tumorigenicity study in rats revealed an increased incidence of testicular tumours.

Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single intraperitoneal injection of azacitidine during organogenesis. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before closure of the hard palate. In rats, azacitidine caused no adverse reactions when given pre-implantation, but it was clearly embryotoxic when given during organogenesis. Foetal abnormalities during organogenesis in rats included: Central nervous system (CNS) anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities).

Administration of azacitidine to male mice prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats resulted in decreased weight of the testes and epididymides, decreased sperm counts, decreased pregnancy rates, an increase in abnormal embryos and increased loss of embryos in mated females (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content
Croscarmellose sodium (E468)
Magnesium stearate (E572)
Mannitol (E421)
Silicified microcrystalline cellulose (E460, E551)

Tablet coating
Opadry II brown containing:
Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Polyethylene glycol/macrogols (E1521)
Triacetin (E1518)
Iron oxide red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The film-coated tablets are packaged in nylon (OPA) / polyvinyl chloride (PVC) aluminium blisters with push through aluminium foil.

Pack size of 7 or 14 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Onureg is a cytotoxic medicinal product. If powder from the film-coated tablets makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If the powder comes in contact with mucous membranes, the area should be thoroughly flushed with water.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15105/0169

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/07/2021

10 DATE OF REVISION OF THE TEXT

24/11/2025