22 April 2021
EMADOC-1700519818-645386
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Copiktra (duvelisib, (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one)
Sponsor: Verastem Europe GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Introductory commnet

The approved therapeutic indication:

"Copiktra monotherapy is indicated for the treatment of adult patients with:

- Relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies
- Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies".

falls within the scope of the two designated orphan conditions chronic lymphocytic leukaemia/small lymphocytic lymphoma and follicular lymphoma. The maintenance of the two respective orphan designations is covered in this one document.

2. Copiktra (duvelisib, (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one) EU/3/13/1125, EMA/OD/0000026423

2.1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	(S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one
Other name(s)	-
International Non-Proprietary Name	Duvelisib
Tradename	Copiktra
Orphan condition	Treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma
Sponsor's details:	Verastem Europe GmbH Lange Strasse 70 29664 Walsrode Lower Saxony Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Voisin Consulting S.A.R.L.
COMP opinion date	13 June 2013
EC decision date	17 July 2013
EC registration number	EU/3/13/1125
Post-designation procedural history	
Transfer of sponsorship	- Transfer from Voisin Consulting S.A.R.L. to Abbvie Ltd - EC decision of 11 November 2015 - 2nd transfer from Abbvie Ltd to Voisin Consulting S.A.R.L. - EC decision of 26 September 2016 - 3rd transfer from Voisin Consulting S.A.R.L. to Verastem Europe GmbH - EC decision of 22 November 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	S. B. Sarac / P. Boudewina van Hennik
Applicant	Verastem Europe GmbH
Application submission date	25 November 2019
Procedure start date	20 January 2020
Procedure number	EMEA/H/C/005381
Invented name	Copiktra

Proposed therapeutic indication	Copiktra monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies. Further information on Copiktra can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Copiktra
CHMP opinion date	25 March 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	K. Pentila / F. Naumann-Winter
Sponsor's report submission date	7 February 2020
COMP discussion and adoption of list of questions	1-3 December 2020
Sponsor's removal request	25 February 2021

2.2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2013 designation was based on the following grounds:

The sponsor Voisin Consulting S.A.R.L. submitted on 11 December 2012 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one for treatment of chronic lymphocytic leukaemia. The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the proposed indication should be amended to "treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma" (hereinafter referred to as "the condition"), in line with the current World Health Organization classification of tumours of haematopoietic and lymphoid tissues;
- the intention to treat the condition with the medicinal product containing (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one was considered justified based on preliminary clinical data showing partial responses in refractory or relapsed patients affected by the condition;
- the condition is life-threatening and chronically debilitating due to development of cytopenias (anaemia, neutropenia, thrombocytopenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections;
- the condition was estimated to be affecting less than 3.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one may be of significant benefit to those affected by the condition. The sponsor has presented preliminary clinical data showing responses in patients previously relapsed or refractory to available treatments. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one as an orphan medicinal product for the orphan indication: treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma.

2.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

CLL/SLL is a lymphoproliferative malignancy characterised by progressive accumulation of morphologically mature but functionally incompetent lymphocytes in the blood, bone marrow, and lymphoid tissues that affects mainly elderly individuals with the median age at presentation of 65 to 70 years. They are both characterized by the presence of small B-lymphocytes that typically express CD5 and CD23 cell surface antigens (Jaffe et al, 2001). Whereas CLL is associated with a leukaemic phase, SLL is characterized by a nodal or solid phase. Based on their similar morphological and immunophenotypic features, the World Health Organization (WHO) classification scheme for haematopoietic malignancies considers CLL and SLL to be different manifestations of the same disease and combines these entities into one disease category (CLL/SLL) (Jaffe et al,2001). The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Moreover, the number of B lymphocytes in the peripheral blood should not exceed 5x109/L (Hallek, 2008).

The approved therapeutic indication "Copiktra monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies" falls within the scope of the designated orphan condition "treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The disease is frequently presented in the elderly, with a median age of 72 years at diagnosis. The condition is life-threatening and chronically debilitating due to development of cytopenias (anaemia, neutropenia, thrombocytopenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections.

The clinical course is highly variable. Some patients survive for decades, whereas others develop aggressive disease and die within several years of diagnosis. Additional markers are available to predict the prognosis of patients with CLL, in particular at early stages. Patients with a detectable del(17p) and a mutation of TP53 (~5% at diagnosis and up to 10% at treatment initiation) have the poorest prognosis, with a median OS of 2–5 years. The prognosis of patients with a del(11q) (~20%) of patients has been strongly improved by chemoimmunotherapy (CTI) with fludarabine, cyclophosphamide and rituximab (FCR) and by targeted agents such as BCRis and venetoclax (ESMO Annals of Oncology 2020). With the new treatment options available, the overall survival (OS) of patients with advanced disease stages has improved.

Number of people affected or at risk

The prevalence estimate proposed by the sponsor is focused on incidence data for CLL only which is derived from assumptions of percentages of CLL of overall leukaemia from 2008 on ECIS 2020 and GLOBOCAN 2018 data. It is assumed that CLL represents 34% of all leukaemias in Europe and that this number has been stable since 2008 (Watson 2008). The COMP considered that this number is now in the range of 38% and that the use of the 2008 publication is not current.

The ESMO 2015 guidelines report median overall survival from diagnosis by stage of disease as follows:

- Binet A: > 10 years
- Binet B: > 8 years
- Binet C: 6.5 years

Eichhorst et al (2009) report the following median survival estimates by diagnosis:

- Binet A: > 10 years
- Binet B: 5 years
- Binet C: 1.53 years.

The prevalence is calculated from incidence and duration (Table 1, Table 2):

Table 1 Point Prevalence Estimates for CLL in the EU

Prevalence Calculations from Incidence and Duration		
Source for Incidence	**Source for duration**	**Estimated prevalence per 10,000**
GLOBOCAN 2018	ESMO 2015	4.53
	Eichhorst et al, 2009	3.91
ECIS 2020	ESMO 2015	4.64
	Eichhorst et al, 2009	4.01

Prevalence Estimates from Reference Databases	
Source	
NORDCAN 2016 (CLL prevalence reported)	5.1
NORDCAN 2016 (CLL prevalence estimated from leukaemia prevalence*)	3.98

*Based on proportion of CLL as 34% of all leukaemias

Table 2 5-year, 10-year Prevalence Estimates for CLL in the EU, UK

Source	5-year Prevalence	10-year Prevalence
GLOBOCAN 2018	3.52	N/A
NORDCAN 2016	2.4	3.85
Haematological Malignancy Research Network 2007-2016 (UK only)	2.95	4.76

The use of data from the ESMO 2015 publication and Eichhorst et al (2009) involves Binet Classification survival rates were based on pre-2006 data. It should be noted that in the updated ESMO CLL/SLL 2020 Guideline the authors state:" *Originally described overall survival times (in the ESMO Guideline from 2015) were deleted because they have changed during the past 30 years [81] but do not reflect the impact of novel treatments*.". The distributions of Binet's stages of CLL are reported in more recent publications as 80% in stage A, 12% in stage B, and 8% in stage C from incident CLL cases described in a publication from 2012 (Tjønnfjord GE 2012). A more current publication by Weide et al 2020 report a change in the Binet stage percentages with Binet A 77%, Binet B 13% and Binet C 5%. These more recent publications highlight the difference and changing nature in the proportions to that presented by the sponsor which are based on an older publication.

The sponsor notes there was an additional publication of survival data in CLL in 2020 (Weide et al, 2020). They state that the data have not been included in the prevalence calculations since the reference is restricted to a German haematology oncology practice and therefore its generalisability to the rest of the EU is unclear. It is also noted by the COMP that a recent publication in the NEJM states that overall survival in the Western World is now 12.7 years for newly diagnosed CLL (NEJM 2020; 383:460-473), therefore the assumption proposed by the sponsor about the limited nature of the Weide et al publication is questionable.

The crude incidence of CLL is on the rise by the demographic change and survival is increasing due to better treatment options. There for the assumption of the percentage being stable at 34% as published in 2008 appears as an underestimate where in fact recent data has shown a percentage of 38% in Germany for example. In addition, current incidence reported for Germany or UK are around 7 in 100,000, questioning the validity of the indirect approach.

The sponsor has also omitted the inclusion of SLL in the prevalence calculation focusing just on CLL. They therefore only consider 74.5% of the incident cases to conclude on a prevalence of CLL. The designated condition is CLL/SLL and the proportion of SLL should be justified.

The COMP in their discussions noted that the epidemiological landscape for CLL/SLL has been changing since 2010. Not only has there been mentioned in Weide et al 2020, NEJM 2020 and ESMO 2020, but also in Haematologica (Baliakas P et al, Letter to the Editor, Haematologica 2018; 103:e158) regarding the change in survival of CLL patients with the introduction of new treatments. The article states: *"A milestone in the management of CLL was the introduction of combined chemoimmunotherapy, in particular the fludarabine-cyclophosphamide-rituximab (FCR) regimen. FCR is the gold standard first-line treatment for medically fit CLL patients except those carrying aberrations of the TP53 gene (TP53abs: i.e. deletion of chromosome 17p, del(17p) and/or TP53 mutations) who should be managed using signaling inhibitors. Additional options, consisting of different combinations of chemotherapeutic agents, anti-CD20 antibodies, signalling inhibitors and the BCL2 inhibitor venetoclax hold promise for further improvement of patients' care."*.

Table 1. Main clinicobiological features of cases treated before and after 2006.

	Treated 1980-2005 n=2093	Treated 2006-2014 n=1411	P
Male	1443/2093, 69%	968/1411, 69%	0.83
Median age at treatment[a](years, range)	63 (22-92)	64.4 (33-92)	0.001
M-CLL	768/2093, 37%	518/1411, 37%	0.99
del(13q)*	323/570, 57%	205/383, 54%	0.33
Trisomy 12*	133/706, 19%	106/495, 21%	0.27
del(11q)*	199/937, 21%	140/676, 21%	0.79
del(17p)*	111/1059, 10%	106/798, 13%	0.063
Subset #2[b]	105/2093, 5%	61/1411, 4%	0.34
Subset #1[c]	68/2093, 3.2%	42/1411, 3%	0.65
Median overall survival	9.5 years	17.5 years	<0.0001

[a]Despite the fact that the two groups have a similar median age, the identified 1.4-year difference emerged as statistically significant due to the variation within groups as well as the large number of cases included in each group. *According to the Döhner hierarchical model, [b]Assignment to stereotyped subset #2, [c]Assignment to stereotyped subset #1.

The proposal made regarding the exclusion of data from Weide et al 2020 appears unsubstantiated. The sponsor did not present updated survival data as well as current data on the proportion of CCL in all leukaemias, so the proposed calculations appear to be under-estimates of the prevalence for CLL.

The COMP has requested a revised more current estimate of the prevalence.

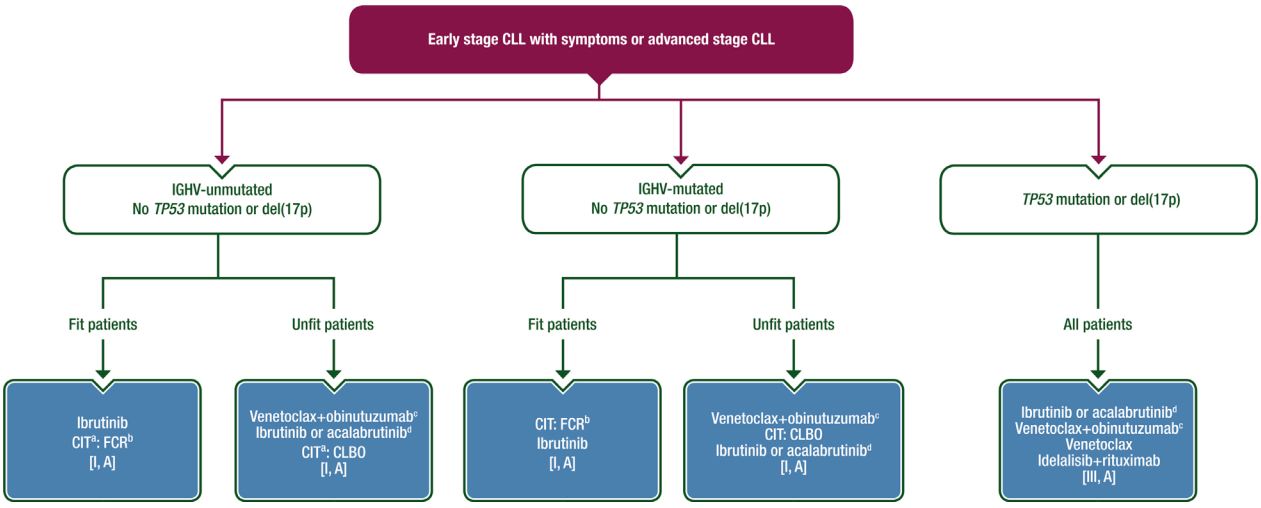
Article 3(1)(b) of Regulation (EC) No 141/2000

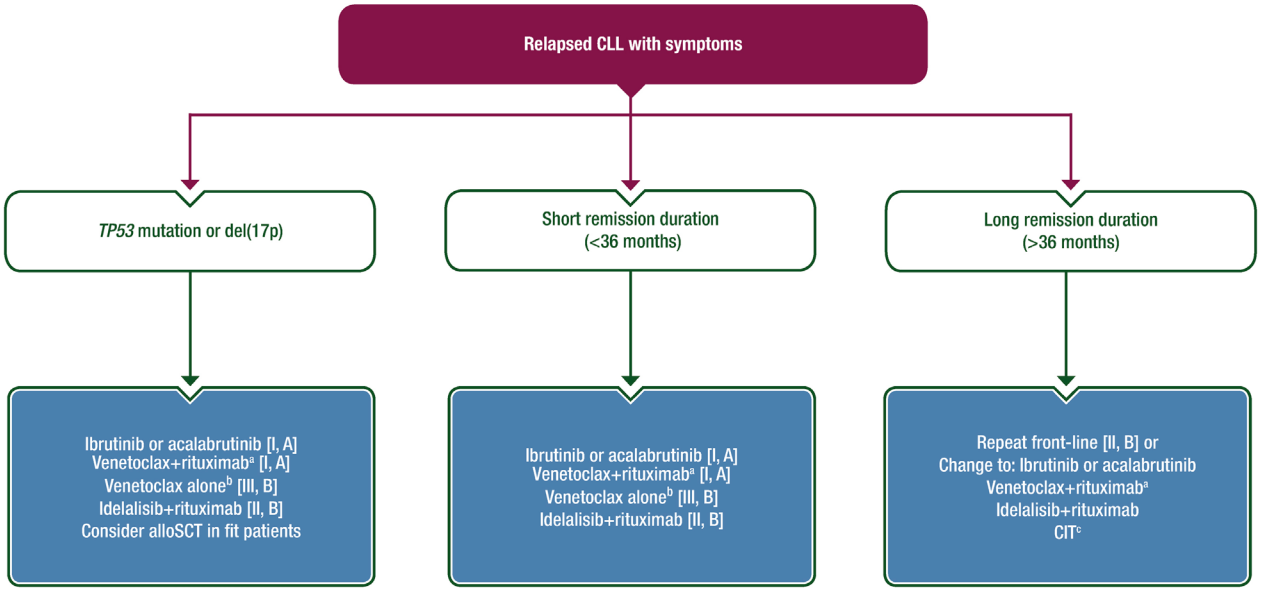
Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor is proposing that several products have been authorised for use in the treatment of patients with CLL/SLL. The products include: chlorambucil, cyclophosphamide, fludarabine (Fludara), alemtuzumab, rituximab (MabThera), ofatumumab (ARZERRA®), bendamustine (Levact, Ribomustin), obinutuzumab (GAZYVARO), ibrutinib (IMBRUVICA®), idelalisib (ZYDELIG®) and venetoclax (VENCLYXTO®).

ESMO has just released new Guidelines in August 2020 (Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, Gregor, M, Cymbalista F, Buske C, Hillmen P, Hallek M, Mey U, on behalf of the ESMO Guidelines Committee, Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up†, Annals of Oncology (2020), doi: https://doi.org/10.1016/j.annonc.2020.09.019.). In this publication new algorithms are proposed in the treatment of CLL/SLL patients.





Significant benefit

Duvelisib, an oral monotherapy, is a dual inhibitor of PI3K-δ and PI3K-γ being proposed for use in relapsed or refractory CLL after at least two prior therapies with or without the presence of 17p

deletion or TP53 mutation. It belongs to the same group of medicines as idelalisib namely phosphoinositide 3-kinase inhibitors.

The sponsor has been to the EMA for scientific advice and a letter dated 19 September 2013 was issued. No question was raised regarding significant benefit. In this submission a claim of significant benefit is being made regarding a target patient population not currently treated with any authorised medicine.

Primary data used to support the CLL/SLL use are provide from the sponsor's pivotal Phase 3 Study IPI-145-07, with additional supportive data from Study IPI-145-06, Study IPI-145-12, and Study IPI-145-02.

Study Number / Key Clinical Data	Design	Population Number of Subjects (n)	Key Efficacy Results
IPI-145-07 Pivotal Efficacy * Safety	Phase 3, Randomised DUV vs OFA	Total: N=319 [a] DUV (n=160) OFA (n=159) Subjects with 17p del or *TP53* mutation: N=101 DUV (n=49[c]) OFA (n=52)	• In the subset of subjects with 2 or more prior therapies: o Median PFS was 16.4 months (95% CI: 12.0, 20.5) for duvelisib versus 9.1 months for ofatumumab (95% CI: 7.9, 10.7), with a hazard ratio of 0.4 (95% CI: 0.27, 0.59) o ORR was 78.9% (95% CI: 70.7, 87.1) for duvelisib versus 38.6% (95% CI: 29.1, 48.1 (p-value<0.001) o The hazard ratio for OS was 0.82 (95% CI: 0.49, 1.37); median OS was not reached for either treatment group • Primary endpoint: duvelisib demonstrated statistically significant superiority over ofatumumab for PFS per IRC assessment (HR = 0.52) o Median PFS = 13.3 months for duvelisib vs 9.9 months for ofatumumab (p<0.0001) • Key secondary endpoint: duvelisib demonstrated statistically significant superiority over ofatumumab for ORR per IRC assessment o ORR = 73.8% for duvelisib vs 45.3% for ofatumumab (p<0.0001) • Key secondary endpoint: OS was similar between the two treatment arms (12-month survival 86% for both treatment arms; HR = 0.99) • LNR (≥ 50% reduction in target lymph nodes from Baseline) significantly favoured duvelisib vs ofatumumab o LNR rate = 85% for duvelisib vs 16% for ofatumumab (p<0.0001) • In subjects with 17p deletion or *TP53* mutation, duvelisib monotherapy resulted in statistically significant improvement in PFS and ORR compared to ofatumumab
			o Median PFS = 12.7 months for duvelisib vs 9.0 months for ofatumumab (HR = 0.4; [95% CI: 0.24, 0.67]) per blinded IRC assessment o ORR = 64.6% for duvelisib vs 40.4% for ofatumumab (p = 0.0126) per blinded IRC assessment
IPI-145-06 Supportive Efficacy * Safety (SLL only)	Phase 2, Single-arm	Total: N=129 SLL: N=28	• ORR per IRC = 67.9% • ORR per Investigator = 85.7% • LNR rate per IRC = 70.4% • LNR rate per Investigator = 82.1%
IPI-145-12 Supportive Efficacy Safety	Phase 3, Open-label Crossover Extension	Total: N=97 DUV (n=89) OFA (n=8) Subjects with 17p del or *TP53* mutation DUV (n=25)	• ORR per Investigator = 73.0% • In subjects with 17p deletion or *TP53* mutation: ORR = 76.0%
IPI-145-02 Supportive Efficacy Safety	Phase 1, Single-arm	Total: N=210 Total CLL/SLL: n=28 [b] CLL/SLL with 17p del and/or *TP53* mutation: n=11	• ORR per Investigator (57.1%) • LNR rate per Investigator (78.6%)

Abbreviations: CLL = chronic lymphocytic leukaemia; DUV = duvelisib; IRC = independent review committee; LNR = lymph node response; OFA = ofatumumab; ORR – overall response rate; OS = overall survival; PFS = progression-free survival; SLL = small lymphocytic lymphoma
*responses assessed per IRC
a. This includes the ITT analysis set (all randomised subjects).
b. Study IPI-145-02 included additional CLL/SLL subjects who received other doses of duvelisib BID: 8 mg, n=1; 15 mg, n=2; 75 mg, n=24.
c. Includes one subject randomised to duvelisib with a *TP53* mutation detected 8 days after initiation of study drug.

The primary objective of pivotal Phase 3 Study IPI-145-07 was to examine the efficacy of duvelisib monotherapy versus ofatumumab monotherapy in subjects with relapsed or refractory CLL or SLL.

This study was a randomized, open-label, parallel design to assess the potential **superiority** of duvelisib treatment over ofatumumab treatment on PFS in subjects with CLL or SLL. The sample size was determined to provide sufficient power to test the primary endpoint of PFS in a group sequential design with 1 planned interim analysis.

A total of 303 subjects with CLL/SLL have received duvelisib 25 mg twice daily (BID) monotherapy across these studies. Of these subjects, 53 subjects had 17p deletion and 11 subjects had 17p deletion or TP53 mutation.

The primary endpoint for the pivotal study (IPI-145-07) was PFS, defined as time from randomisation to the first documentation of progressive disease per blinded IRC or death due to any cause. CLL disease progression was determined according to modified IWCLL criteria (Hallek et al, 2008), and SLL disease progression according to modified IWG criteria (Cheson et al, 2007).

The results from the 4 clinical studies used for evaluating duvelisib monotherapy 25 mg BID in subjects with CLL/SLL, showed acceptable clinical activity across the studies.

For the purpose of establishing significant benefit the sponsor claimed that the data show the benefit for duvelisib is most favourable in the subset of patients receiving 2 or more prior therapies.

The sponsor was asked to discuss the possible detrimental effect of duvelisib in select patients with 17p-del given the higher number of deaths in this treatment arm.

In line with the ESMO CLL Guideline with relation to risk assessment, the sponsor performed an analysis of PFS in patients with 17p- and/or TP53 mutation (48 in the duvelisib arm and 52 in the ofatumumab arm). The median PFS for subjects randomised to duvelisib was 12.7 months (95% CI: 9.0, 21.9) and 9.0 months (95% CI: 5.5, 10.8) ($p = 0.0002$) for ofatumumab. The hazard ratio for duvelisib vs ofatumumab was 0.40 (95% CI: 0.24, 0.67), thus in line with the 17p-only population.

Since 2014, novel targeted agents have been approved in the relapsed setting which includes the indication of CLL in patients with 17p deletion or TP53 mutation. Of these, idelalisib (ZYDELIG® SmPC, 2014) and venetoclax (VENCLYXTO® SmPC, 2019) are authorised for use after relapse from one prior line of therapy.

The sponsor has provided data in patients who have received two prior lines of therapy. The current proposed indication at CHMP is:

COPIKTRA monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies.

Currently there are no treatments for patients after two relapses to either acalabrutinib/ibrutinib, venetoclax, venetoclax+rituximab or idelalisib+rituximab in any of the three subsets described in the most up to date ESMO CLL/SLL Guidelines from August 2020. Although some indirect comparisons to idelalisib and venetoclax have been presented in the submission their value in establishing the clinically relevant advantage is more of informative nature, as neither have the indication for the target patient population the proposed indication is seeking to obtain.

The sponsor has also provided data on patient's refractory to or with an early relapse after purine analogue-based therapy who have a dismal prognosis. In study IPI-145-07 the median PFS for these patients for duvelisib was 10.4 months (95% CI: 9.0, 16.6) and for ofatumumab 8.1 months (95% CI:

3.4, 10.4)). The hazard ratio for duvelisib vs ofatumumab was 0.51 (95% CI: 0.27, 0.96). In patients not refractory/early relapse to prior purine analog-based therapy the median PFS for duvelisib was 15.1 months (95% CI: 12.7, 17.8) and for ofatumumab 10.8 months (95% CI: 9.3, 12.6). The hazard ratio for duvelisib vs ofatumumab was 0.53 (95% CI: 0.38, 0.73).

The COMP discussed whether significant benefit was met in the proposed target patient population, or if further indirect comparative data is needed versus the combinations proposed in the new ESMO 2020 Guidelines in relapsed CLL/SLL patients. In their deliberations the COMP considered that the patient population included in the trials did not seem to reflect current medical practice with more recently authorised products. The Committee considered that additional justification was needed to further clarify if the clinical results presented really could support significant benefit and thus a question was raised.

2.4. COMP list of issues

Prevalence

The sponsor is asked to re-address the prevalence of the proposed condition in the EU, taking into account the "Points to consider on the estimation and reporting of the prevalence of a condition for orphan designation"

The sponsor is asked to recalculate the prevalence as no current data regarding the incidence and overall survival has been provided for this incurable disease. Sensitivity analyses on all assumptions should be conducted as the prevalence of CLL/SLL is very close to the threshold. These should include contemporary crude incidence and the impact of current treatment on survival and should therefore clarify the complete prevalence of CLL/SLL.

Significant Benefit

The sponsor is invited to further elaborate the significant benefit of their product in the target patient population of double relapsed refractory CLL/SLL. The patient population on which the authorised therapeutic indication is based does not appear to be representative of current patients with double relapsed or refractory disease. The sponsor should further elaborate on the place of their product within the context of currently authorised products and to discuss its significant benefit for patients previously treated according to standard of care (ibrutinib, acalabrutinib, venetoclax or idelalisib).

3. Copiktra (duvelisib, (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one) EU/3/13/1157, EMA/OD/0000024085

3.1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	(*S*)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one
Other name(s)	-
International Non-Proprietary Name	Duvelisib
Tradename	Copiktra
Orphan condition	Treatment of follicular lymphoma
Sponsor's details:	Verastem Europe GmbH Lange Strasse 70 29664 Walsrode Lower Saxony Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Voisin Consulting S.A.R.L.
COMP opinion date	13 June 2013
EC decision date	17 July 2013
EC registration number	EU/3/13/1157
Post-designation procedural history	
Transfer of sponsorship	- Transfer from Voisin Consulting S.A.R.L. to Abbvie Ltd - EC decision of 11 November 2015 - 2nd transfer from Abbvie Ltd to Voisin Consulting S.A.R.L. - EC decision of 26 September 2016 - 3rd transfer from Voisin Consulting S.A.R.L. to Verastem Europe GmbH - EC decision of 22 November 2019
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Rapporteur / Co-rapporteur	S. B. Sarac / P. Boudewina van Hennik
Applicant	Verastem Europe GmbH
Application submission date	25 November 2019
Procedure start date	20 January 2020
Procedure number	EMEA/H/C/005381
Invented name	Copiktra

Proposed therapeutic indication	Copiktra monotherapy is indicated for the treatment of adult patients with follicular lymphoma (FL) that is refractory to at least two prior systemic therapies. Further information on Copiktra can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Copiktra
CHMP opinion date	25 March 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	K. Pentila / F. Naumann-Winter
Sponsor's report submission date	7 February 2020
COMP discussion and adoption of list of questions	1-3 December 2020
Sponsor's removal request	25 February 2021

3.2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2013 designation was based on the following grounds:

The sponsor Voisin Consulting S.A.R.L. submitted on 25 March 2013 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing *(S)*-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one for treatment of follicular lymphoma (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing *(S)*-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one was considered justified based on preliminary clinical data in patients with advanced follicular lymphoma;
- the condition is life-threatening due to a median survival of approximately 8 to 10 years following diagnosis;
- the condition was estimated to be affecting 3.6 in 10,000 persons in the European Union, at the time the application was made; this was based on data obtained from the GLOBOCAN 2008 register.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing *(S)*-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with advanced follicular lymphoma that demonstrate that their product induced

complete and partial responses. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing *(S)*-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one, as an orphan medicinal product for the orphan indication: treatment of follicular lymphoma.

3.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Follicular lymphoma (FL) is an indolent B cell lymphoproliferative disorder of transformed follicular center B cells consisting of a mixture of centrocytes (small to medium-sized cells) and centroblasts (large cells), mixed with nonmalignant cells such as T cells, follicular dendritic cells and macrophages.

Almost all FLs carry breaks at 18q21, with > 85% of them having a translocation involving chromosomes 14 and 18 (t[14;18][q32;q21]). The t(14;18) translocation ultimately results in the juxtaposition of the apoptosis regulating gene B-cell lymphoma (BCL) 2 on chromosome 18 with the IGH transcriptional enhancer of immunoglobulin heavy-chain locus on chromosome 14. This leads to the constitutive overexpression of BCL-2, which blocks apoptosis and gives the cells a survival advantage.

The aetiology of follicular lymphoma is still poorly understood. It has been suggested that age, gender and ethnicity may affect a person's likelihood of developing follicular lymphoma. The incidence increases with age; although in principle follicular lymphoma may occur at any age, it is extremely rare in children.

Follicular lymphoma involves lymph nodes, but also spleen, bone marrow, peripheral blood and Waldeyer ring. Involvement of non-haematopoietic extranodal sites, such as the gastrointestinal tract or soft tissue may occur in a setting of widespread nodal disease. Follicular lymphoma may occasionally be primary in extranodal sites, including skin, gastrointestinal tract, particularly the duodenum, ocular adnexa, breast and testis.

Most patients have widespread disease at diagnosis, including peripheral and central (abdominal and thoracic) lymphadenopathy and splenomegaly. The bone marrow is involved in 40-70% of cases. As an intrinsic disease characteristic, FL typically evolves over time to an aggressive subtype, in 45% of cases. Disease relapse is usually rapid, where remissions become a serious challenge despite multiple interventions. Eventually, patients succumb to the refractory, high-grade disease transformation and the complications driven by treatments.

The approved therapeutic indication "Copiktra monotherapy is indicated for the treatment of adult patients with follicular lymphoma (FL) that is refractory to at least two prior systemic therapies" falls within the scope of the designated orphan condition "treatment of follicular lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

No changes have occurred in the chronically debilitating and life-threatening nature of the condition since the designation. Follicular lymphoma remains life-threatening and chronically debilitating, mainly due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation into aggressive lymphoma.

Number of people affected or at risk

The sponsor provided a limited prevalence calculation based on relevant incidence data but combined with outdated assumptions which do not display the evolving nature of FL prevalence.

The sponsor does not state an exact estimate for prevalence, only that it is "less than 5 per 10,000". It is proposed that FL constitutes approximately 17-25% of all NHLs (Trask et al, 2012; Hübel et al. 2020). Non-Hodgkin lymphoma (NHL) is the twelfth most frequently diagnosed malignancy in the EU, with 86,321 incident cases estimated in 2020 (ECIS, 2020, EU27).

GLOBOCAN 2018 and ECIS 2020 data are used for calculation. As data for FL is not available, data for NHL is used. The sponsor assumes that the proportion of FL of all NHL cases is between 17 and 25% (Trask 2012 → no FL proportion stated in this publication; Hubel 2020 → FL represents "20 – 30% of all NHL cases"). 17, 20 and 25% are used for sensitivity analysis.

As ECIS data is more current than GLOBOCAN data, and both databases refer to the IARC data, a detailed description of the sponsor's calculation based on ECIS data is provided.

ECIS data is presented as absolute figures for each EU-27 country separately, added to get the total number of NHL cases in EU-27 (86,321) and divided by the EU population of 2018 according to Eurostat (446,105,649). Crude NHL incidence: 19.35/100,000.

Median survival is estimated as 10 years (Freedman 2018).

Using the FL/NHL proportions of 17, 20 and 25%, respectively, and the duration of 10 years, the prevalence is calculated as **3.29, 3.36 and 4.20** per 10,000.

This calculation is not correct. The correct results are:

P = I (19.35/100,000) * D (10y) * 17% (FL/NHL) = **3.2895** per 10,000

P = I (19.35/100,000) * D (10y) * 20% (FL/NHL) = **3.87** per 10,000

P = I (19.35/100,000) * D (10y) * 25% (FL/NHL) = **4.8375** per 10,000

These estimates still lie below the threshold of 5 per 10,000. However, the stated duration/overall survival of FL (10 years) is questionable.

In the reference given by the sponsor (Freedman, 2018), the Swedish Lymphoma registry is cited, which reports 10y-OS rates between 64 and 92% (depending on age group). These figures are clearly

higher than 50%. mOS data are not stated in this publication, at least not for the total FL population (but, e.g., for early stage disease with up to 19 years).

Several other publications report that mOS is approaching 20 years (Provencio et al., 2017: mOS not reached, but over 20y; Batlevi et al. 2020: US data, mOS not reached, but 10y-OS is 80%, and 15y-OS is 65%).

Even if: 1.) the correct EuroSTAT population is used (2020, not 2018), which leads to a slightly lower NHL incidence of 19.28/100.000; 2.) a proportion of 20% FL/NHL is used, which is the lower estimate in the references given by the sponsor; and 3.) a duration of disease of 15 years is assumed which seems to be a realistic/rather low estimate; the result is a prevalence of **5.7 per 10,000**.

Additionally, the sponsor states some prevalence estimates:

Prevalence Estimates from Reference Databases	
Source	**Estimated prevalence per 10,000**
NORDCAN 2016*	2.86
Orphanet	3.33
ECIS 2020 age-specific rates (ASR)*	
European new	4.58
European old	3.23
World	2.85

*Based on FL proportion of NHL of 20-25%

As NHL total prevalence in NORDCAN 2016 is 17.5/10,000, it is not clear how the sponsor calculated the 2.86 figure (highlighted in yellow), which corresponds to 16.3% of 17.5, and not to "20-25%".

The ECIS data shown in the table is the ASR for 2020 incidence, not prevalence, assuming a FL/NHL proportion of 25%.

The proposed prevalence estimate proposed by the sponsor appears to be an underestimate of the current situation in the EU. As a result, the COMP has requested a revised estimate of the prevalence of the Follicular Lymphoma.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

As reported by the sponsor, the clinical course of follicular lymphoma is characterized by recurrences requiring multiple lines of treatment until eventually patients run out of treatment options and develop fatal disease resistant to any available treatment.

The most recent (2016) guidelines from the European Society of Medical oncology (ESMO) (Dreyling et al., Annals of Oncology 27 (s5)v83-90) can be considered valid, and recommend:

First-line treatment

A minority of patients will present with non-bulky stage I/II at diagnosis, since most patients are diagnosed when the lymphoma is already at advanced stage. These patients may benefit from radiotherapy, and in selected cases, watchful waiting or rituximab monotherapy. In stage I–II patients

with large tumour burden, adverse clinical or biological prognostic features or when local radiotherapy is not applicable (e.g. lung, liver), systemic therapy as indicated for advanced stages should be applied for patients in stage III/IV, who represent the majority of patients with naïve follicular lymphoma, the ESMO guidelines recommend start treatment only in the presence of symptoms. The current standard first-line treatment of advanced FL is induction with chemoimmunotherapy (e.g., R-CHEMO) followed with 2-year maintenance with rituximab monotherapy (around a 30-month treatment in total).

Relapsed follicular lymphoma (FL)

Relapsed FL is the target of this lenalidomide extension. The treatment options in this setting include rituximab monotherapy, a R CHEMO regimen that the patient did not receive previously (e.g., R Benda, R CHOP, R CVP) with or without rituximab maintenance, idelalisib, bendamustine, bendamustine plus obinutuzumab, and ibritumomab tiuxetan. The currently authorized treatments in the EU and their therapeutic indications are: rituximab, interferon alfa-2b, Y90 ibritumomab tiuxetan, bendamustine, idelalisib, obinutuzumab, lenalidomid.

Significant benefit

Duvelisib is an oral, dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and -ɣ developed as a monotherapy for the treatment of adult patients with relapsed or refractory FL. Currently the CHMP is considering the following indication: *Copiktra monotherapy is indicated for the treatment of adult patients with Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies*.

On 9 April 2014, COMP (EMA/COMP/79140/2014) adopted the advice to give to the prior applicant on the potential for demonstrating significant benefit in the proposed study IPI-145-08 in patients with FL as discussed with SAWP on 04 February 2014. Concern was noted by the agency in using rituximab monotherapy as the comparator because it was only approved for FL in the frontline setting in combination with chemotherapy.

Current ESMO Guidelines indicate that idelalisib is authorised for used in double refractory FL patients. *In later relapses, monotherapy is an established option with palliative intent. The PI3K inhibitor idelalisib has been registered in double-refractory FL, based on a phase II study.*

The current idelalisib SmPC states that: *Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.*

The COMP noted the similarities between both the sponsor's proposed indication and that for Zydelig.

To support their claim for significant benefit the sponsor has provided clinical data which has been used to support the Marketing Authorisation Application currently in CHMP.

Study Number / Key Clinical Data	Design	Population Number of Subjects (n)
IPI-145-07 Pivotal Efficacy Safety	Phase 3, Randomised DUV vs OFA	Total: N=319 [a] DUV (n=160) OFA (n=159) Subjects with 17p del or *TP53* mutation: N=101 DUV (n=49[c]) OFA (n=52)
IPI-145-06 Supportive Efficacy Safety	Phase 2, Single-arm	Total: N=129 FL: N=83
IPI-145-12 Supportive Efficacy Safety	Phase 3, Open-label Crossover Extension	Total: N=97 DUV (n=89) OFA (n=8) Subjects with 17p del or *TP53* mutation DUV (n=25)
IPI-145-02 Supportive Efficacy Safety	Phase 1, Single-arm	Total: N=210 FL at 25 mg BID: n=13

Abbreviations: DUV = duvelisib; OFA = ofatumumab

The CHMP report has highlighted the similarity of this product to two other products used in the same line of treatment of follicular lymphoma.

Idelalisib, a PI3K-δinhibitor was granted approval as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment based on the results of a single arm trial demonstrating durable complete and partial responses, (Study 101-09, DELTA, NCT01282424) (Zydelig SmPC, Gopal et al., 2014) and extension Study 101-99, NCT01090414). In this single-arm study, idelalisib demonstrated an overall response rate (ORR) of 54.2% (8.3% complete response [CR], 45.8% partial response [PR]) in 72 FL subjects (Zydelig SmPC). The median duration of response (DOR) for FL subjects was not reached. Confirmation of clinical benefit has not yet been reported in a randomised controlled setting. The ESMO Clinical Practice Guidelines for Newly Diagnosed and Relapsed Follicular Lymphoma include idelalisib as a recommended treatment option for later relapses providing an alternative monotherapy treatment for patients with FL that are refractory to rituximab or alkylating agents (Dreyling et al., 2016).

Another anti-CD20 antibody, obinutuzumab, was approved in April 2016 in combination with bendamustine followed by obinutuzumab maintenance in patients with FL who have relapsed or who are refractory to a rituximab-containing regimen by demonstrating improved progression-free survival (Gazyvaro SmPC).

The CHMP also has noted that:

It is noted that duvelisib has not been evaluated in patients who relapsed or were refractory for idelalisib since patients which were pre-treated with PI3Kδ inhibitors were excluded from the clinical studies.

And it was also noted that:

The treatment landscape has changed over time as discussed in the efficacy section. The pivotal studies were performed in a study population, which does not exist anymore. Patients previously

treated with PI3 kinase inhibitors or BTK inhibitors (e.g. idelalisib and ibrutinib) were excluded from the pivotal studies.

And,

Of note, the treatment landscape of R/R FL has changed since start of the pivotal trial (24 June 2013) with the PI3K inhibitor idelalisib as treatment option for double-refractory FL (ESMO guideline 2016). The applicant requests for an indication in adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. The studied population consisted mostly of FL patient's refractory to rituximab and chemotherapy (e.g. double refractory) and no previous PI3 kinase treatment. This patient population has become very rare due to changes in the treatment landscape.

The sponsor claims that idelalisib is different from duvelisib. They propose that the purine group serves as the hinge binder for binding of inhibitor. A new specificity pocket is created according to "quinazolinone moiety" in case of idelalisib and according to "isoquinolinone moiety" in case of duvelisib. The plasticity of p110δ may enable this isoform to accommodate even very rigid compounds more readily. It is also proposed that opening of the specificity pocket might be easier in p110δ compared to p110γ, and selectivity is at least partially a reflection of energy required to open the specificity pocket.

The sponsor concluded that the "isoquinolinone moiety" unique to duvelisib contributes to its therapeutic activity, as compared to idelalisib, which has a "quinazolinone moiety". It is therefore noted that duvelisib and idelalisib are PI3K inhibitors that represent distinct therapeutic moieties, which result in these two medicinal products displaying a different inhibitor profile. In addition, the respective major metabolites of these compounds have the correspondingly different structures.

A recent publication indicates that this difference may not be so important and groups these products together stating that PI3K inhibitors represent an important class of novel CLL/SLL and FL therapies. PI3K is a well-recognized biologic target in cancer. Four class I PI3K catalytic isoforms are expressed in mammalian tissue (p110α, β, γ, and δ). While p110δ/β isoforms are expressed ubiquitously, p110γ/δ isoforms are predominantly expressed in immune cells. (Blood. 2019;134(19):1573-1577). This article describes duvelisib as a second-generation oral inhibitor of phosphoinositide-3 kinase, downstream of the B-cell receptor pathway. Additionally, the review article provides a comparative efficacy table in follicular lymphoma of duvelisib to the idelalisib and copanlisib. This has been based on registration studies according to the authors and as such show that there are some differences regarding ORR and PFS between duvelisib and idelalisib which question the real benefit of the different conformational blocking presented by the sponsor.

Table 2. PI3K inhibitors in FL

All patients (patients with FL)	Duvelisib (PI3Kγ,δ)[13]	Idelalisib (PI3Kδ)[14]	Copanlisib (PI3Kα,δ)[15]
	129 (83)	125 (72)	142 (104)
Median prior therapies (range)	3 (1-10)	4 (2-12)*	3 (2-9)*
Median time since progression, mo (range)	3.2	NA	8.3 (1-73)*
ORR, %	42	57*	59
CR, %	1	6	14
PR, %	41	50	44
SD, %	34.9		34
PFS, mo	9.5	11*	11.2
Discontinued due to adverse events, %	31*	20*	25*
Key grade ≥3 adverse events with frequency >10%	Neutropenia, diarrhea, anemia, thrombocytopenia	Neutropenia, diarrhea, ALT elevation	Hyperglycemia, hypertension, neutropenia, pneumonia

ALT, alanine aminotransferase.
*Whole study population.

It is noted in their submission that the sponsor has not provided a direct or indirect comparison to idelalisib. They have only discussed the need for a therapy in the area of double-refractory follicular lymphoma patients. While it is interesting that there are some molecular differences between idelalisib and their product duvelisib this is insufficient to establish the significant benefit.

The COMP therefore raised a question on significant benefit.

3.4. COMP list of issues

Prevalence

The sponsor has proposed a prevalence which appears to be an under-estimate being based on a lower assumption of the percentage non-Hodgkin lymphomas as well as survival which does not reflect the current understanding. The sponsor should provide a new estimate based on more current assumptions in Europe as well as a sensitivity analysis.

Significant benefit

The claim for significant benefit is based on a targeted patient population which is double relapsed refractory. The sponsor has not provided a direct or indirect comparison to idelalisib which has the same indication to establish significant benefit. The sponsor is invited to further elaborate on the comparative efficacy of these two products which are authorised in the same patient population.