APPENDIX

A phase 2 study of parsaclisib, a PI3Kδ inhibitor, in relapsed and refractory follicular lymphoma (CITADEL-203)

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Supplemental Tables

Table S1: **Schedule of study assessments**

	Screening	Treatment			EOT	Follow-up		
						Safety	Disease	Survival
Procedure	**Day −28 to −1**	**Day 1***	**Every 4 weeks through week 48 (± 3 days)**	**Every 12 weeks from week 48 (± 1 week)**		**EOT + 30–35 days**		**Every 12 weeks (± 1 week)**
Informed consent	X							
Contact IWRS	X	X	X	X	X			
Inclusion, exclusion criteria	X	X						
Demography, medical history	X							
HR-QOL FACT-Lym		X	Every 8 weeks through week 24 (± 1 week), then every 12 weeks through week 96, and then every 24 weeks thereafter until PD			X	X†	
Prior/concomitant medications	X	X	X	X	X	X		
AE assessment	X	X	X	X	X	X		
Comprehensive physical examination	X‡				X			
Disease-specific physical examination		X	X	X		X		
Vital signs	X	X	X	X	X	X		
12-lead ECG	X	X	X§	X	X	X		
ECOG PS	X	X	X	X	X	X		
CT/MRI scan	X‖		Every 8 weeks through week 24 (± 1 week), then every 12 weeks through week 96, and then every 24 weeks thereafter until PD				X†	
Bone marrow examination	X¶							
PJP prophylaxis		X**						
Study drug dispensing		X	X	X				
Study drug compliance		X	X	X	X			
Study drug administration at site		X	X††					
Disease follow-up							X†	
Survival follow-up								X‡‡

AE=adverse event. CR=complete response. CT=computed tomography. ECG=electrocardiogram. ECOG PS=Eastern Cooperative Oncology Group performance status. EOT=end of treatment. FACT-Lym=Functional Assessment of Cancer Therapy-Lymphoma. HRQOL=health-related quality of life. IWRS=interactive web-response system. MRI=magnetic resonance imaging. PD=progressive disease. PJP=*Pneumocystis jiroveci* pneumonia. PK=pharmacokinetics.

*All procedures are to be performed before administration of study treatment. †Only for patients who discontinue study treatment for reasons other than disease progression. Radiologic imaging and health-related quality of life will continue to be performed per assessment schedule (every 8, 12, or 24 weeks as appropriate) until disease progression. ‡Height required at screening only. §Week 4, week 12, and every 12 weeks thereafter. ‖If CT is not available, is not practicable, or is contraindicated, then an MRI may be substituted. Every effort must be made to use the same modality for disease assessment throughout the study for each individual patient. Lesion assessment must be done for the neck, chest, abdomen, and pelvis. ¶Required at baseline except for reasons provided in the protocol. If disease is present in bone marrow at baseline, a bone marrow biopsy is required to confirm CR. **PJP prophylaxis will continue for 2–6 months after the last dose of study treatment. ††Only on days when PK samples are taken: day 1 and week 4 for both treatments, and week 12 for the daily dosing group.

‡‡May be conducted by telephone or email.

Table S2: **Patient disposition and exposure as of Jan 15, 2021 cut-off**

	Weekly dosing group* (n=23)	**Daily dosing group (n=103)**	**All treated patients (N=126)**
Patients discontinued from treatment	19 (83)	68 (66)	87 (69)
Primary reasons for discontinuing			
Progressive disease	13 (56.5)	33 (32)	46 (36.5)
Adverse event	4 (17)	23 (22)	27 (21)
Withdrawal/physician decision	2 (9)	11 (11)	13 (10)
Death	0	1 (1)	1 (1)
Patients with ongoing treatment, n (%)	4 (17)	35 (34)	39 (31)
Median (range) duration of treatment,† months	9.6 (0.45–27.2)	8.4 (0.8–27.2)	8.5 (0.5–27.2)
Median (range) duration of follow-up,‡ months	26.3 (10.0–34.1)	17.6 (5.7–33.1)	20.6 (5.7–34.1)

*Includes 11 patients who switched to 2.5 mg once-daily parsaclisib after starting the 20 mg once-weekly period. †Duration of treatment (months)=(date of last dose – date of first dose + 1) / 30.4375; drug interruptions were included in the duration of treatment. ‡Duration of follow-up (months)=(cut-off date [Jan 15, 2021] – first dose date + 1) / 30.4375.

Table S3: **Most common any grade and grade ≥3 TEAEs (occurring in ≥10% of patients) and corresponding grade ≥3 TEAEs among patients receiving parsaclisib in the weekly dosing group**

Preferred term, n (%)	Weekly dosing group* (n=23)	
	Any grade	Grade ≥3
Any TEAE	23 (100)	13 (56.5)
Nausea	6 (26.1)	0
Rash	6 (26.1)	1 (4.3)
Diarrhoea	3 (13.0)	1 (4.3)
Cough	3 (13.0)	0
Fatigue	3 (13.0)	0
Vomiting	3 (13.0)	0
Anaemia	3 (13.0)	2 (8.7)
Upper respiratory tract infection	3 (13.0)	0
Urinary tract infection	3 (13.0)	0

QD=once daily. QW=once weekly. TEAE=treatment-emergent adverse event.

*Includes 11 patients that switched to 2.5 mg QD parsaclisib after starting the 20 mg QW period.

***Table S4*: Treatment-Emergent adverse events of special interest in the daily dosing group**

	Weekly dosing group* (n=23)		Daily dosing group (n=103)		Total (n=126)	
Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Diarrhoea	3 (13)	1 (4.3)	45 (43.7)	14 (13.6)	48 (38.1)	15 (11.9)
Rash	6 (26)	1 (4.3)	14 (13.6)	3 (2.9)	20 (15.9)	4 (3.2)
Colitis	0	0	9 (8.7)	7 (6.8)	9 (7.1)	7 (5.6)
Pneumonia	1 (4.3)	0	5 (4.9)	2 (1.9)	6 (4.8)	2 (1.6)
Pneumonitis	1 (4.3)	1 (4.3)	2 (1.9)	2 (1.9)	3 (2.4)	3 (2.4)
CMV infection	0	0	3 (2.9)	1 (1.0)	3 (2.4)	1 (0.8)
Exfoliative dermatitis	0	0	2 (1.9)	1 (1.0)	2 (1.6)	1 (0.8)
Febrile neutropenia	0	0	2 (1.9)	2 (1.9)	2 (1.6)	2 (1.6)
PJP infection	0	0	1 (1.0)	1 (1.0)	1 (0.8)	1 (0.8)

BTKi, Bruton's kinase inhibitor; CMV, cytomegalovirus; PJP, *Pneumocystis jirovecii* pneumonia
*Includes 11 patients that switched to 2.5 mg once-daily parsaclisib after starting the 20 mg once-weekly period.

Table S5: **Selected new or worsening haematologic and chemistry laboratory abnormalities in the weekly dosing group**

Preferred term, n (%)	Weekly dosing group* (n=23)		
	Any grade	Grade 3†	Grade 4†
Neutrophils decreased	10 (43.5)	2 (8.7)	1 (4.3)
Haemoglobin decreased	6 (26.1)	1 (4.3)	N/A
Platelets decreased	5 (21.7)	0	0
ALT increased	7 (30.4)	0	0
AST increased	5 (21.7)	0	0

NA=Common Terminology Criteria for Adverse Events grade not applicable to the parameter.
ALT=alanine aminotransferase. AST=aspartate aminotransferase. QD=once daily. QW=once weekly.
*Includes 11 patients that switched to 2.5 mg QD parsaclisib after starting the 20 mg QW period.
†Worst grade post-baseline reported for each patient

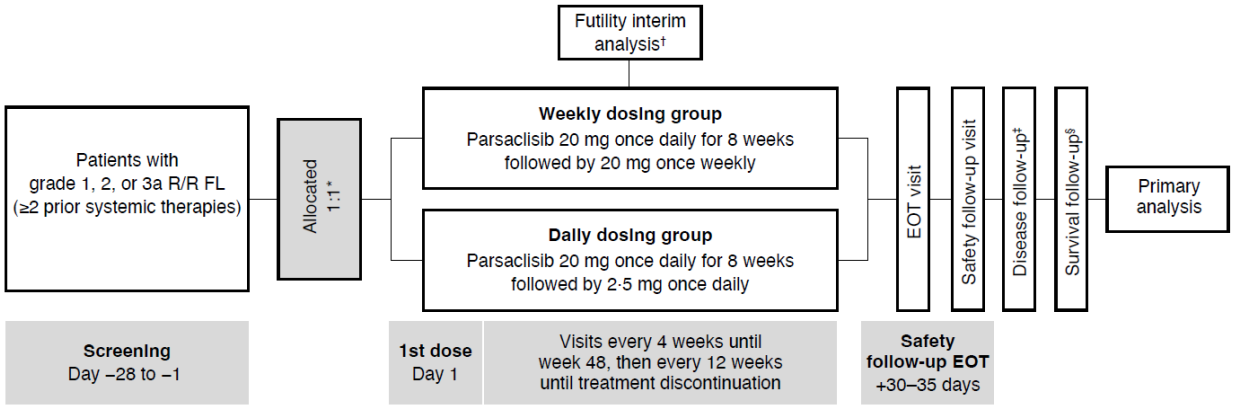
Table S6: **Differentially expressed analytes at week 4 of parsaclisib treatment compared with baseline**

Analyte	Reduction from baseline* (N=108) % (95% CI)
TNFRSF9	−76.5 (−79.2 to −73.4)
FCER2	−76.3 (−80.7 to −70.8)
CXCL13	−70.6 (−74.35 to −66.4)
CCL19	−68.2 (−72.0 to −63.8)
TNFRSF4	−66.9 (−70.8 to −62.5)
LTA	−63.5 (−67.5 to −58.9)
IL10	−63.2 (−68.4 to −57.1)
CCL17	−62.4 (−68.9 to −54.55)
IL10	−60.9 (−66.35 to −54.6)
TNFRSF13B	−59.5 (−65.1 to −52.9)
FCRL2	−56.4 (−62.0 to −49.9)
IL2RA	−53.05 (−58.2 to −47.3)
LAIR2	−52.9 (−57.65 to −47.6)
L12B	−48.4 (−52.75 to −43.7)
CD160	−46.75 (−49.7 to −43.7)
XCL1	−44.35 (−48.1 to −40.3)
MMP9	−42.9 (−48.6 to −36.6)

Differentially expressed analytes were all in common with Study INCB 50465-101.
CI=confidence interval.
*1 – Geometric mean of (% from baseline).

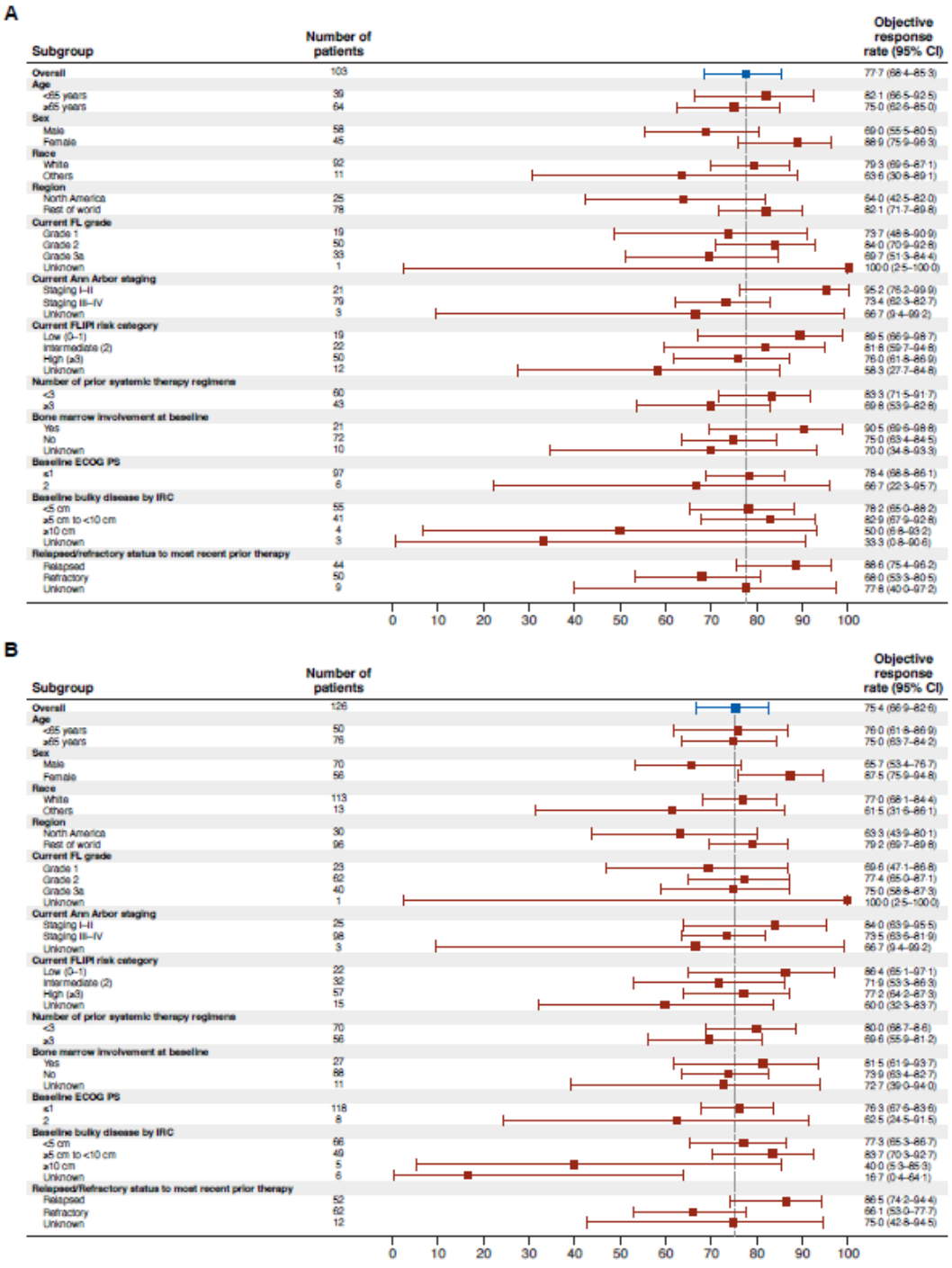
Supplemental Figures

Figure S1: **CITADEL-203 study design**



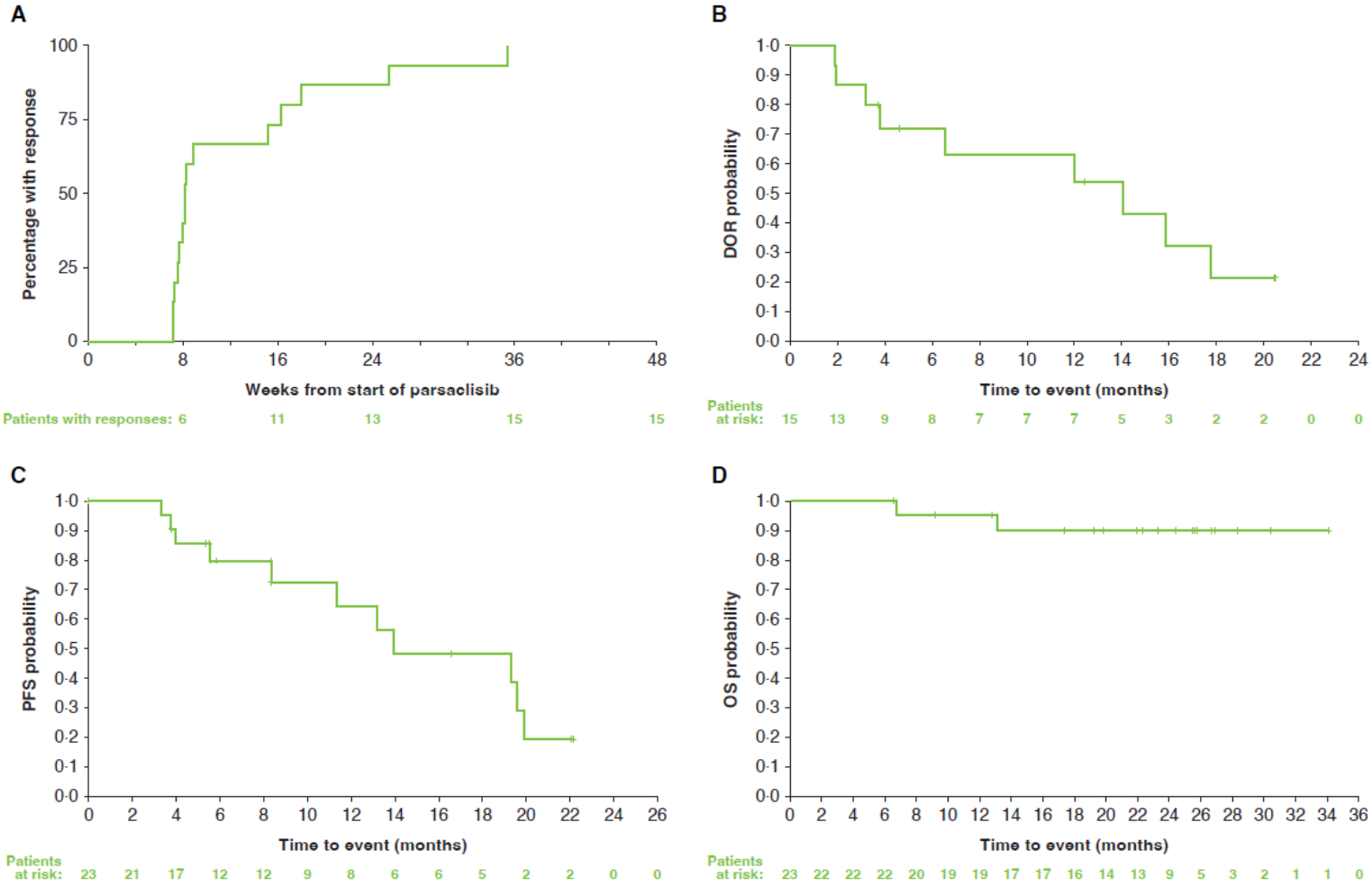
EOT=end of treatment. FL=follicular lymphoma. R/R=relapse/refractory.
*The first 50 patients were planned to be allocated in a 1:1 ratio to the weekly dosing group and daily dosing group. The remaining 70 patients were planned to be enrolled in the selected treatment group (daily dosing group). †Futility analysis was performed when the first 50 patients were evaluated for a response. ‡Only patients who discontinued study treatment for reasons other than disease progression continued with disease assessments by radiologic imaging per protocol every 8, 12, or 24 weeks as appropriate until disease progression. §Every 12 weeks by telephone or email.

Figure S2: **Forest plot of objective response rate by subgroup in the (A) daily dosing group and (B) all treated patients by independent review committee (IRC) review**



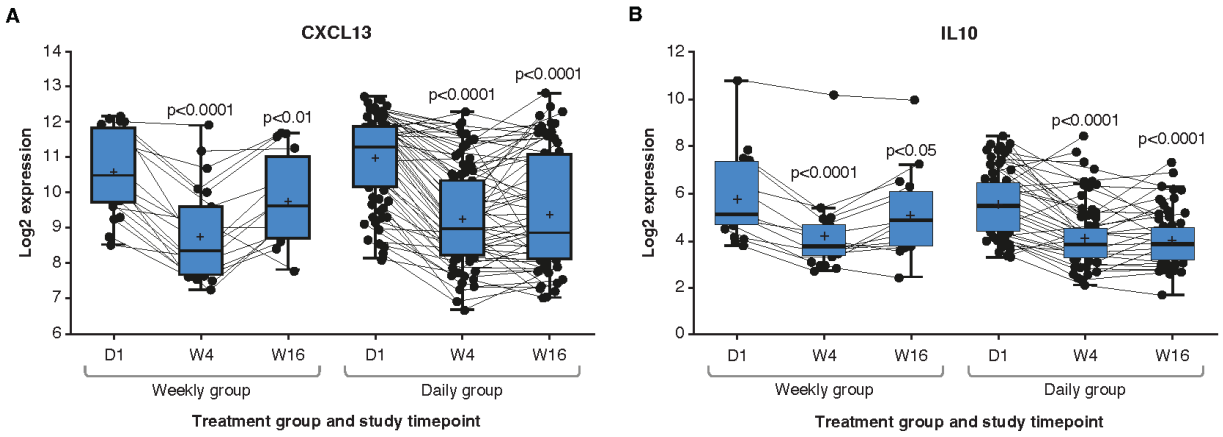
Squares represent estimates of objective response rate and error bars represent 95% CI.
CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. FL=follicular lymphoma. FLIPI=Follicular Lymphoma International Prognostic Index.

Figure S3: **(A) Cumulative time to response curves, and (B) Kaplan-Meier estimates of duration of response (DOR) and (C) progression-free survival (PFS) by independent review committee, and (D) overall survival (OS) in the weekly dosing group***



*Includes 11 patients who switched to 2.5 mg once-daily parsaclisib after starting the 20 mg once-weekly period.

Figure S4: **Expression of serum CXCL13 and IL10 at baseline and at weeks 4 and 16 after treatment with parsaclisib.**



Log2 values of CXCL13 and IL10 at baseline (D1), week 4 (W4), and week 16 (W16) for Treatment A and Treatment B were plotted. The boxes denote first and third quartiles, lines indicate the median, and whiskers indicate maximum and minimum values. False discovery rate p-values were determined by paired t-test comparing each timepoint to paired values at baseline (cycle 1 day 1).
IL=interleukin.