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SUPPORTING INFORMATION

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Real-life observational cohort verifies high efficacy of dupilumab for chronic rhinosinusitis with nasal polyps

To the Editor,

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) is a primary, diffuse CRS-phenotype, in the Western world having a type-2 (T2) endotype predominance.[1] With 85% of CRS-patients belonging to the working-age population, it constitutes a vast economic burden to society. Productivity losses from absenteeism and presenteeism are the major cost expense, followed by healthcare consumption.[2] Despite optimal care, a subpopulation of CRSwNP-patients remains insufficiently controlled. Biologicals targeting T2-pathway components have recently been registered for severe, uncontrolled CRSwNP. This new and promising treatment modality has been implemented in the integrated CRS care pathways, alongside (updated) assessment criteria for current clinical CRS-control and response to biologicals of CRSwNP.[1,3] Dupilumab, blocking IL-4 and IL-13 by targeting IL-4Rα, is registered for CRSwNP via the registration trials LIBERTY NP SINUS (LNPS)-24 and LNPS-52.[4] Recent systematic review and appraisal further concluded dupilumab efficacious, although cost-effectiveness remains undissolved and insufficient data heretofore impedes head-on comparison to other agents.[5,6] We report our provisional findings from a real-life, prospective observational cohort, aimed to evaluate the therapeutic efficacy of add-on dupilumab as the primary biological therapy in an adult CRSwNP-population (≥18y) in our tertiary referral center, and to verify the EPOS2020 biologicals indication criteria. Eligible patients from this cohort with ≥12w follow-up, until and including May 2021, were included in this study. Dupilumab was auto-administered subcutaneously, 300mg 1x/2 weeks (Q2W). Stepwise interdose interval prolongation (SIIP) by 2w ensued in those with moderate to excellent response, with minimal 24w-interim periods, thus proceeding the successfully explored SIIP in LNPS-52 (officially off-label dosing interval; full methodology in Supplements). Mean scores of all primary outcomes improved significantly from baseline (n=131) to the 24w (n=98) and 48w (n=26) timepoints: SinoNasal Outcome Test-22 (SNOT-22, 0 – 110) improved from 52.4 (*s.d.*: *19.6*) to 18.5 (*12.9*) and 16.8 (*12.4*), respectively; bilateral Nasal Polyp Score (NPS, 0 – 8) improved from 5.4 (*2.0*) to 1.6 (*1.7*) and 1.0 (*1.7*); Sniffin' Sticks-12 identification test (SSIT-12; 0 – 6 anosmia, 7 – 10 hyposmia, 11 – 12 normosmia) improved from 3.6 (*2.1*) to 7.3 (*2.8*) and 8.3 (*3.2*); if applicable, asthma control test (ACT, 5 – 25) improved from 17.8 (*4.6*), to 21.8 (*3.4*) and 23.5 (*1.9*), increasing the rate of well-controlled asthma from 45.6% at baseline to 76.8% and 94.1%, respectively (Table 1 & Figure 1a-d). At baseline, CRS was controlled in 0%, partly controlled in 4.2%, and uncontrolled in 95.8%. At 24w and 48w, respectively, 75.7% and 93.8% were partly controlled, and 24.3% and 6.2% were uncontrolled; "controlled CRS" was unachievable with biologicals considered rescue treatment (Table 1 & Table S1). Rescue treatment otherwise was applied in two cases (oral corticosteroids and no antibiotics). Four patients ceased treatment, due to non-responsiveness (1); subjective insufficient control (1); persistent hypereosinophilia (1); and possible treatment emergent

TABLE 1 Therapeutic outcome of dupilumab treatment in patients with chronic rhinosinusitis.

	This study	LIBERTY NP SINUS−52				LIBERTY NP SINUS−24		
	24w: q2w		24w: q2w			24w: q2w		
Endpoints at 24 weeks	**(n = 98)**	**change from BL**	**(n = 295)**	***p****	**change from BL**	**(n = 143)**	***p****	**change from BL**
Nasal Polyp Score (NPS; 0–8)								
Mean	1.56 (1.74)	3.67 (2.30)	4.46 (1.89)	<0.001	1.71 (1.89)	3.75 (1.98)	<0.001	1.89 (1.67)
NPS: 0	39 (39.8%)							
NPS: 1	13 (13.3%)							
NPS: 2	27 (27.6%)							
NPS: 3 – 4	12 (12.2%)							
NPS: 5 – 6	7 (7.1%)							
NPS: 7 – 8	0 (0.0%)							
≥1 point change in BL	81 (82.7%)		183 (62.0%)			93 (65.0%)		
≥2 points change in BL	78 (79.6%)		136 (46.1%)			66 (46.2%)		
Modified LK-score (0–20)	3.6 (2.5)	5.9 (3.9)						
Smell test score[1]	7.3 (2.8)	3.87 (2.96)	23.89 (9.21)		9.71 (9.62)	25.39 (9.49)		11.26 (8.01)
Trinomial olfactory functioning[2]								
Anosmia	34 (34.7%)		84 (30.0%)			33 (23.9%)		
Hyposmia	50 (51.0%)		163 (58.1%)			82 (59.3%)		
Normosmia	14 (14.3%)		33 (11.8%)			23 (16.7%)		
Olfactory functioning improvement								
≥ 1 level	59 (60.2%)							
1 level	48 (49.0%)							
2 levels	11 (11.2%)							
SNOT−22 score (0–110)	18.49 (12.90)	31.35 (19.20)	23.89 (18.77)	0.002	27.77 (21.6)	18.58 (14.92)	0.960	30.43 (18.42)
PNIF (0–300 L/min)	137.30 (41.64)	47.30 (37.49)	55.29 (52.9)	<0.001	36.63 (28.0–45.3)	54.50 (64.1)	<0.001	40.41 (30.4–50.4)
EPOS2020 CRS control								
Controlled	0 (0.0%)							
Partly controlled	56 (75.7%)							
Uncontrolled	18 (24.3%)							
EPOS2020 biological response								
No response	0 (0.0%)							
Poor response	3 (3.7%)							
Good response	45 (55.6%)							
Excellent response	33 (40.7%)							

(Continues)

TABLE 1 (Continued)

Endpoints at study's end[3]	48w: q2w&q4w (n = 26)		52w: q2w-q4w (n = 150)		
Nasal Polyp Score (NPS; 0–8)					
Mean	1.04 (1.66)	3.74 (2.78)	3.76 (2.20)	<0.001	2.24 (2.58)
NPS: 0	14 (53.8%)				
NPS: 1	2 (7.7%)				
NPS: 2	4 (15.4%)				
NPS: 3 – 4	2 (7.7%)				
NPS: 5 – 6	1 (3.8%)				
NPS: 7 – 8	0 (0.0%)				
≥1 point change in BL	19 (82.6%)				
≥2 points change in BL	16 (69.6%)				
Modified LK-score (0–20)	2.9 (2.1)	6.1 (3.5)			
Smell test score[1]	8.3 (3.2)	4.1 (3.0)			
Trinomial olfactory functioning[2]					
Anosmia	7 (30.4%)				
Hyposmia	11 (47.8%)				
Normosmia	5 (21.7%)				
Olfactory functioning improvement					
≥1 level	14 (60.9%)				
1 level	10 (43.5%)				
2 levels	4 (17.4%)				
SNOT–22 score (0–110)	16.75 (12.35)	35.50 (19.00)	21.67 (19.16)	0.094	29.84 (28.0)
PNIF (L/min)	150.00 (29.54)	47.83 (29.69)			
EPOS2020 CRS control					
Controlled	0 (0.0%)				
Partly controlled	15 (93.8%)				
Uncontrolled	1 (6.2%)				
EPOS2020 biological response					
No response	0 (0.0%)				
Poor response	0 (0.0%)				
Good response	12 (48.0%)				
Excellent response	13 (52.0%)				

Note: Values are reported as mean (standard deviation), unless otherwise indicated. Standard deviations of the LIBERTY NP SINUS (LNPS) studies were calculated from the reported standard mean errors. Two decimal values are displayed for measures that could be compared to the LNPS studies, which reported as such. Percentages reported for this study are calculated over the proportion of patients with available data. Means reported for LNPS studies are least square means.

* *p* reported for unpaired t test, compared to this study.1: Sniffin' Sticks-12 in this study, UPSIT-40 in the LNPS studies. 2: hyposmia in the LNPS studies is denoted as pooled mild, moderate, and severe microsmia. 3: The studies' endpoint differ, that is, 48 v.s. 52 weeks. BL: baseline; CRS: chronic rhinosinusitis; EPOS2020: European Positioning Paper on Rhinosinusitis and Nasal Polyps, edition 2020; MLKES: Modified Lund-Kennedy Endoscopy Score; PNIF: Peak Nasal Inspiratory Flow; qNw: once every N weeks; SNOT-22: SinoNasal Outcome Test-22.

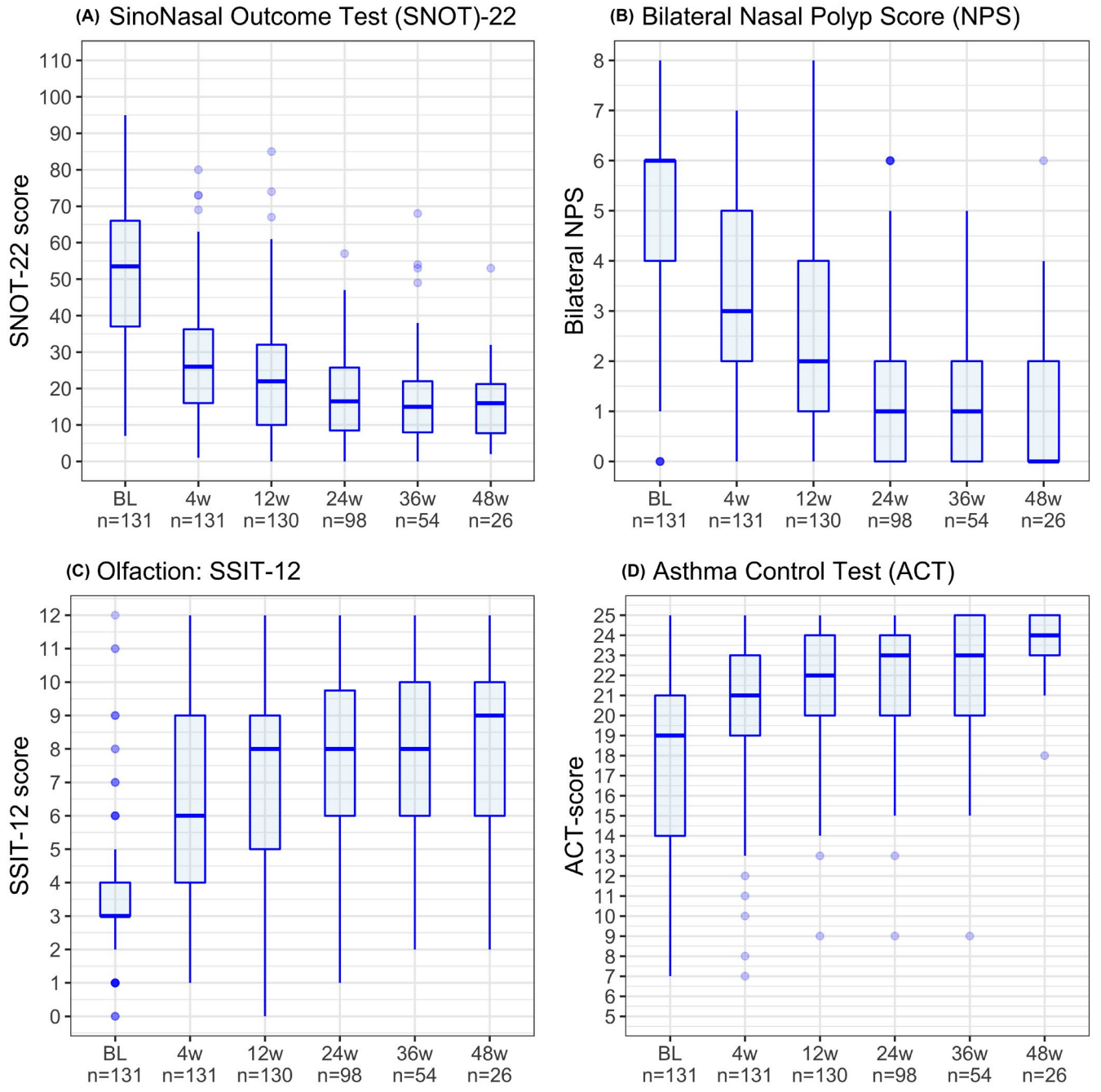

FIGURE 1 a-d. Boxplots displaying improvement of (A) SinoNasal Outcome Test-22, (B) bilateral Nasal Polyp Score, (C) Sniffin' Sticks-12 identification test, and (D) Asthma Control Test during dupilumab treatment for chronic rhinosinusitis with nasal polyps (CRSwNP). ACT: Asthma Control Test; BL: baseline; NPS: Nasal Polyp Score; SNOT-22: SinoNasal Outcome Test-22; SSIT-12: Sniffin' Sticks-12 identification test; w: weeks

serious adverse event (1), that is, pericarditis (unverifiable treatment relation, see Supplement). Of patients continuing treatment, 96.3% demonstrated moderate to excellent response at 24w and 100% at 48w. Importantly, a protocol deviation appeared retrospectively in the non-responsive patient, not satisfying the T2-criterion, underlining its importance in relation to the mechanism of action. SIIP to Q4W was applied from 24w and 36w onwards in 72/98 (73.5%) and 49/54 (90.7%) patients, respectively, and from 48w onwards to Q4W in 14/26 (53.8%) and to Q6W in 12/26 (46.2%), provisionally indicating continued established control and/or improvement of CRSwNP during SIIP up to these frequencies/timepoints. Treatment emergent adverse events occurred in about half of the patients. They were mild and decreased in occurrence and intensity throughout treatment (see also Supplements). This cohort's indication (EPOS2020-based) differs essentially from the preceding LNPS-trials (mainly depending on NPS).[4]

Baseline demographics were comparable, besides those related to indication. Therapeutic effects were comparable or slightly favorable in this cohort, validating the EPOS2020 indication criteria as minimally equivalent. The strength of this study lies in the real-life context, reporting on a prospective cohort with standardized indication criteria, treatment regimen, and follow-up schedule. The therapeutic outcome has been monitored throughout almost a year, enabling evaluation of its dynamics throughout this period. Limitations apply as well. Selection bias may have occurred, for example, due to this study's setting (tertiary referral center), and by reporting on the first cohort of patients, possibly comprising the patients with the most severe and difficult-to-treat CRSwNP. Evaluation of succeeding clusters and future inclusion of non-academic patient cohorts will elucidate this matter. Concluding, this first large, real-life, prospective observational cohort study verifies add-on dupilumab therapy as highly efficacious in the treatment of difficult-to-treat, type-2 inflammation-driven CRSwNP, concurrently validating the applied EPOS2020 indication criteria for biological treatment.

KEYWORDS

biological therapy, dupilumab, observational study, sinusitis, treatment outcome

The patient registry PolyREG, dedicated to observational scientific research of patients treated with biologicals for chronic rhinosinusitis with nasal polyps and associated comorbidity, from which subcohort this study reports, is co-funded by Sanofi and Novartis.

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CONFLICT OF INTEREST

WF and SR are advisory board members of Sanofi and Novartis. WF has acted as a consultant and guest speaker for Sanofi, Novartis, and GSK. SR has acted as a consultant for Sanofi and Novartis. RL has acted as a consultant for GSK.

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