

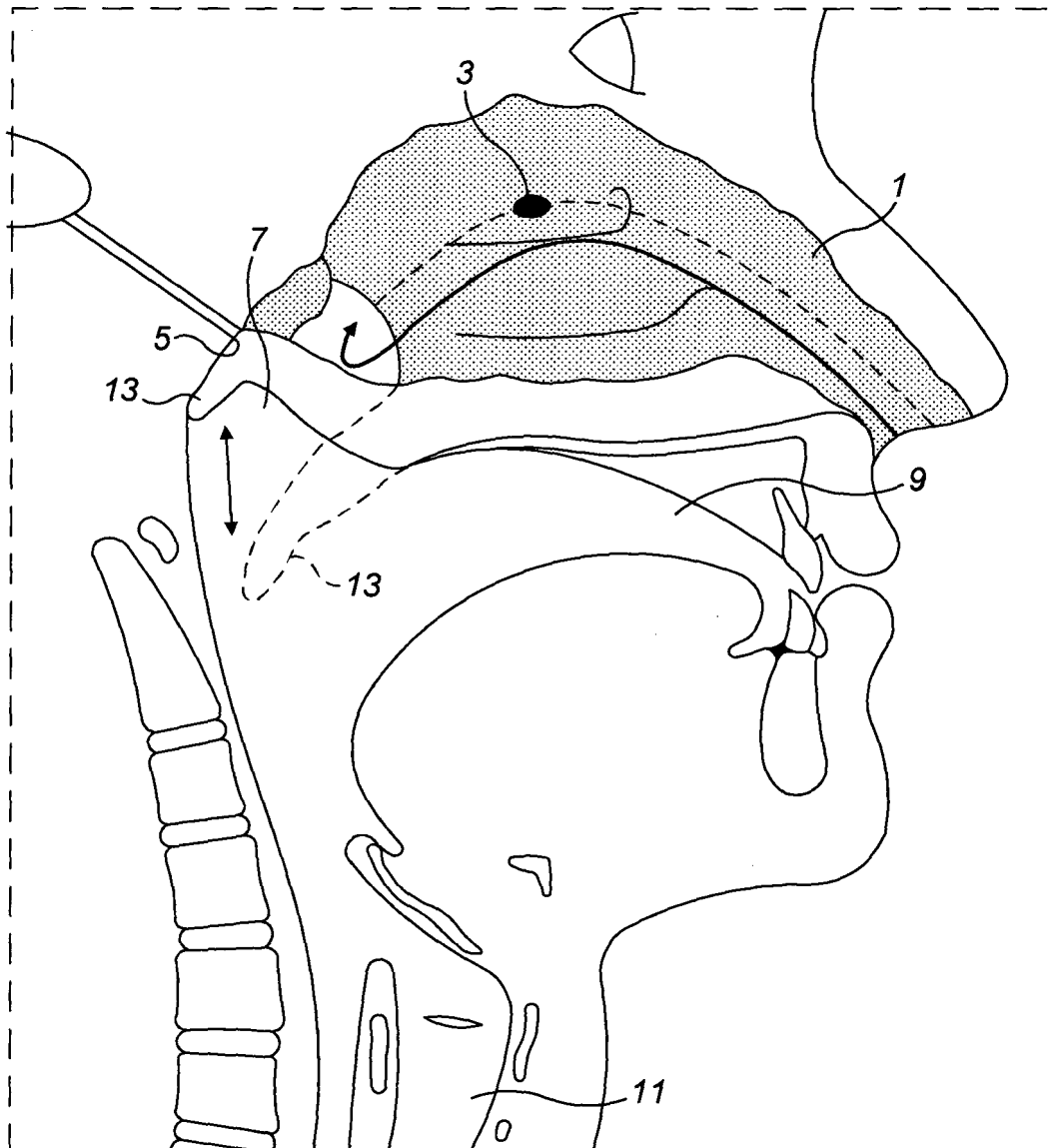


FIG. 1(a)

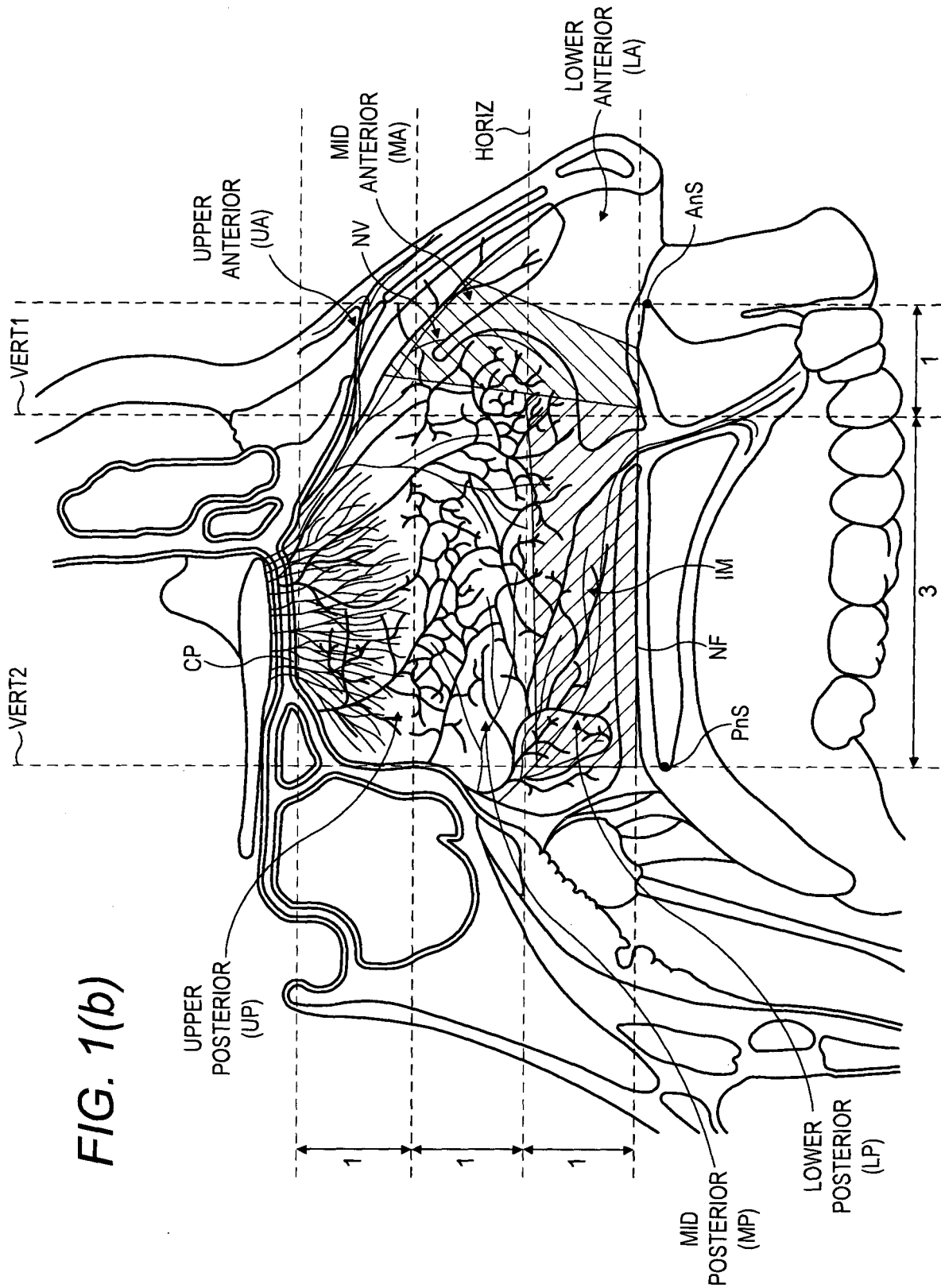


FIG. 1(b)

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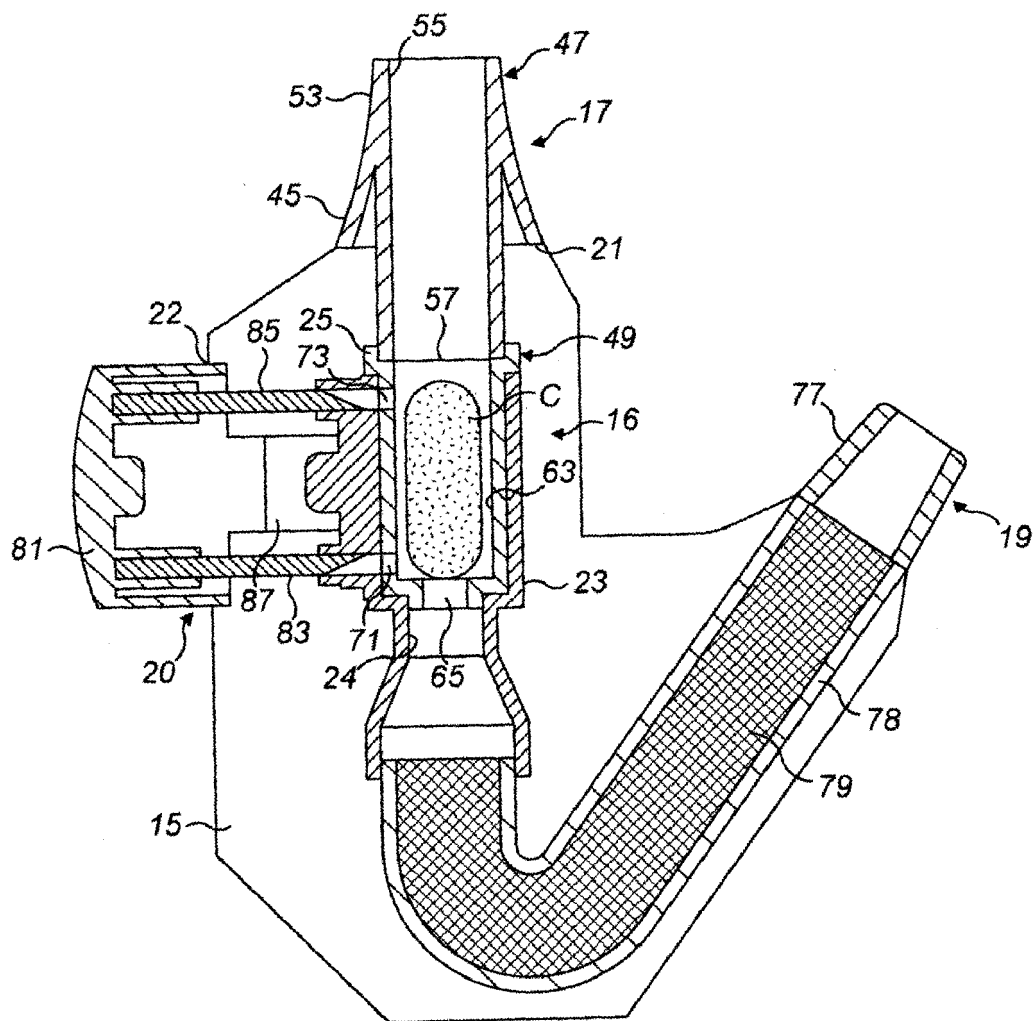


FIG. 2(a)

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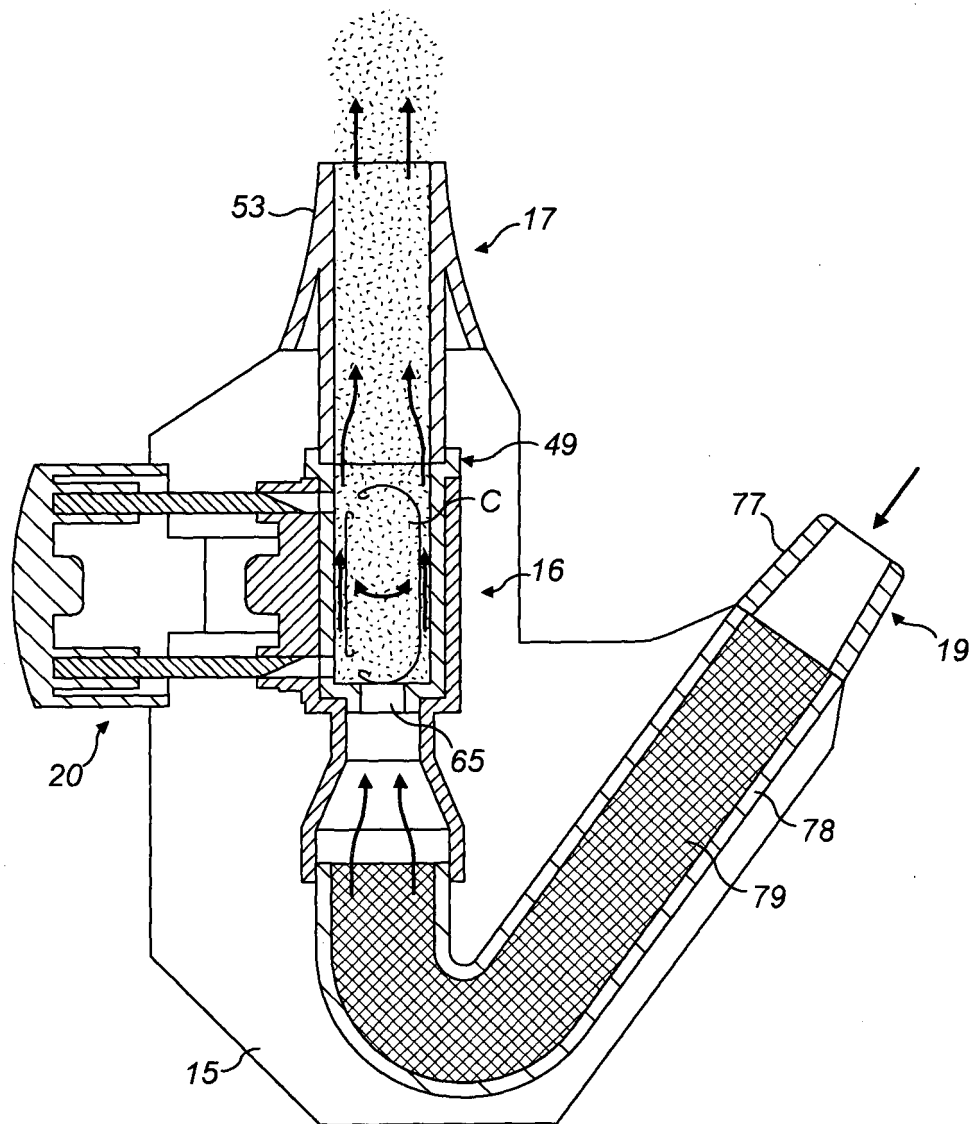


FIG. 2(b)

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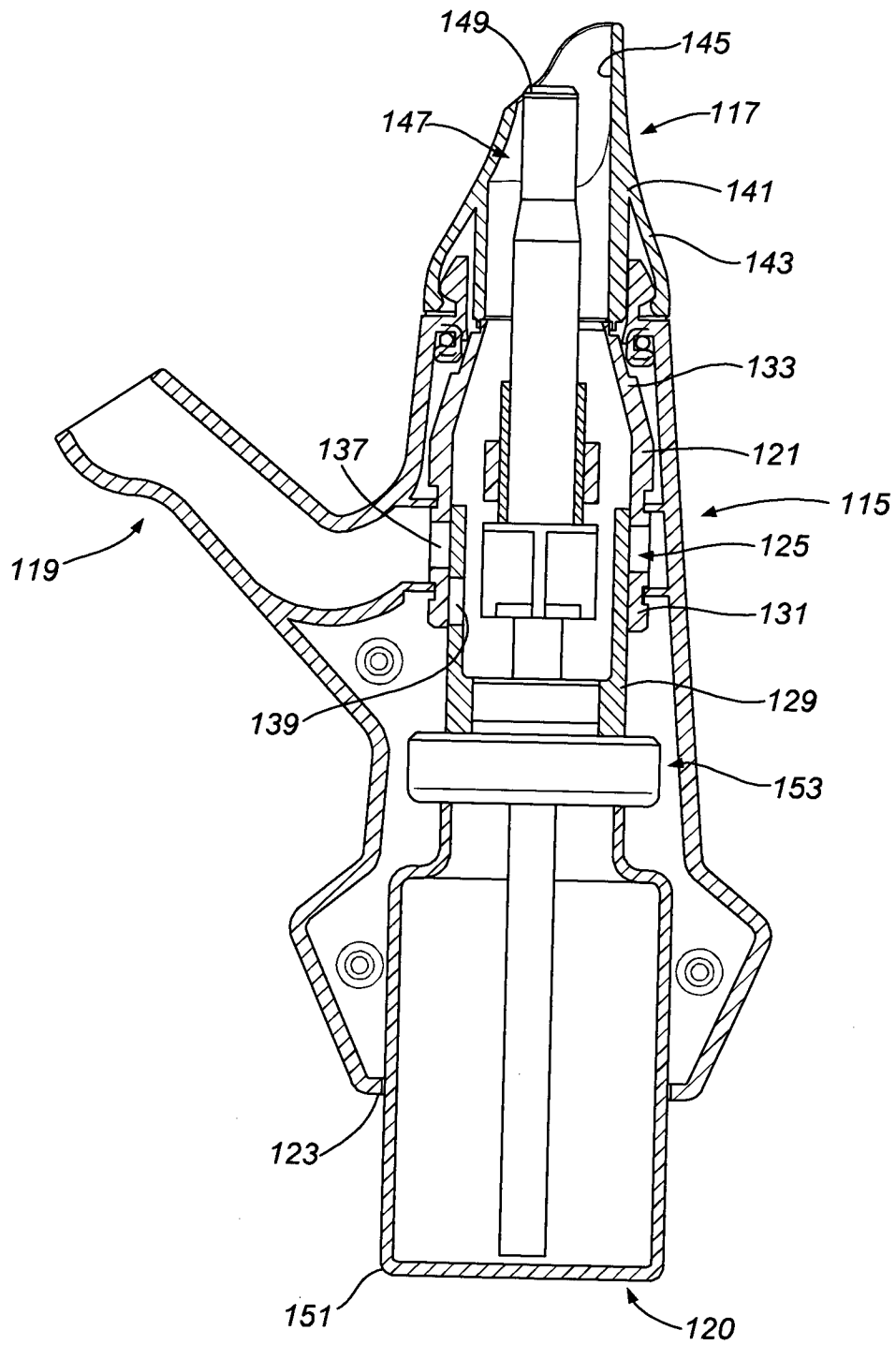
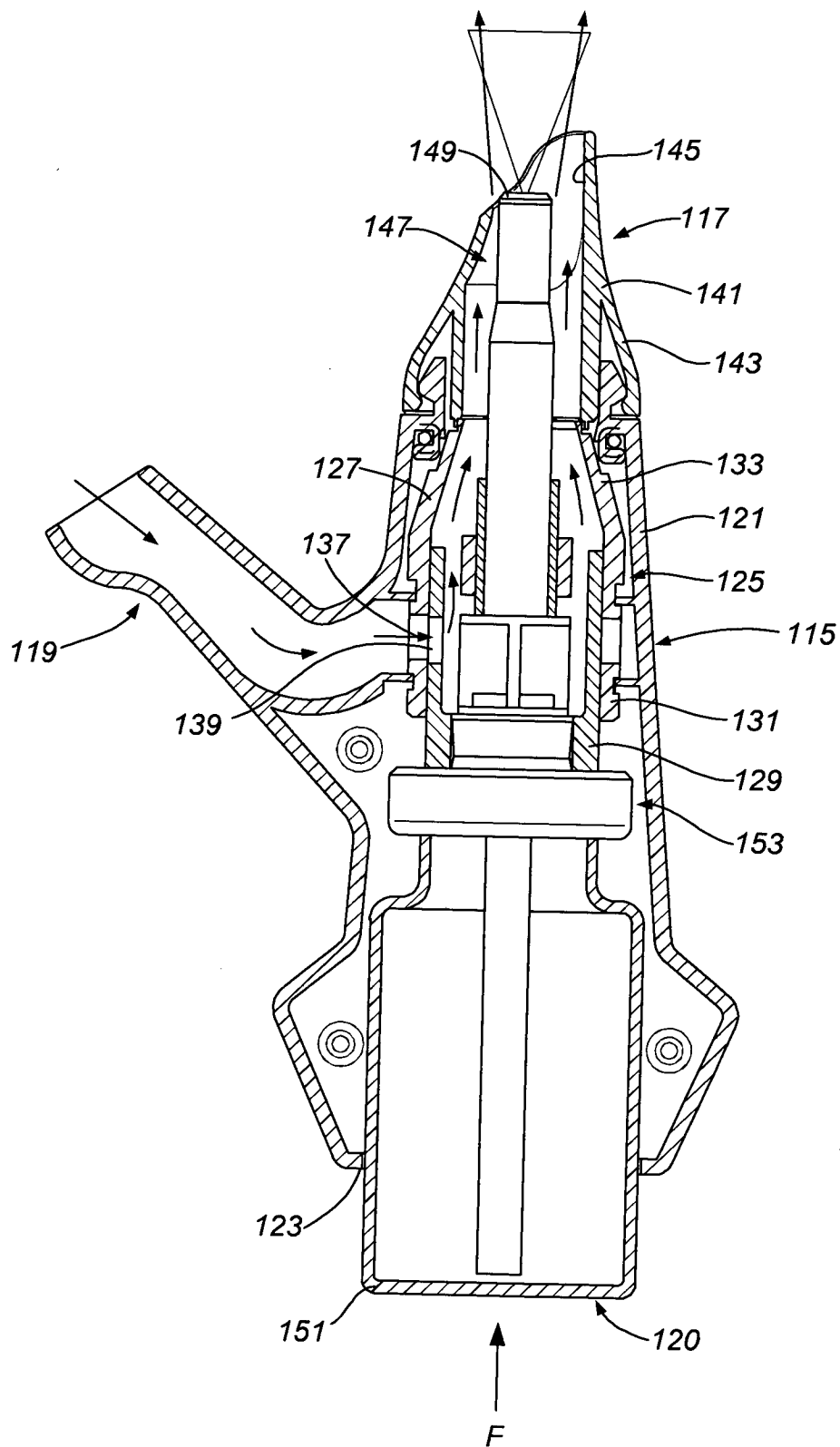


FIG. 3(a)

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**FIG. 3(b)**

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Parameter	Description
$C_{\max}$	maximum observed drug concentration
$t_{\max}$	time to reach $C_{\max}$
AUC_{0-t}	area under the drug concentration-time curve from time zero to time t , where t is the time of the last measurable concentration $[C_p]$, calculated using the linear trapezoidal rule
$AUC_{0-\infty}$	area under the drug concentration-time curve from time zero to infinity, calculated as $AUC_{0-\infty} = AUC_{0-t} + C_p/\lambda_z$
$AUC_{0-15 \text{ min}}$	area under the drug concentration-time curve from time zero to 15 minutes
$AUC_{0-30 \text{ min}}$	area under the drug concentration-time curve from time zero to 30 minutes
$t_{1/2}$	terminal elimination half-life, calculated as $\ln(2)/\lambda_z$ where λ_z is the apparent first-order terminal elimination rate constant calculated from a semi-log plot of the concentration vs time curve by linear least-squares regression analysis
λ_z	terminal elimination rate constant
$AUC_{\% \text{extrap}}$	percentage of $AUC_{0-\infty}$ extrapolated from C_p to infinity, calculated as $100 \times [1 - (AUC_{0-t}/AUC_{0-\infty})]$

FIG. 5

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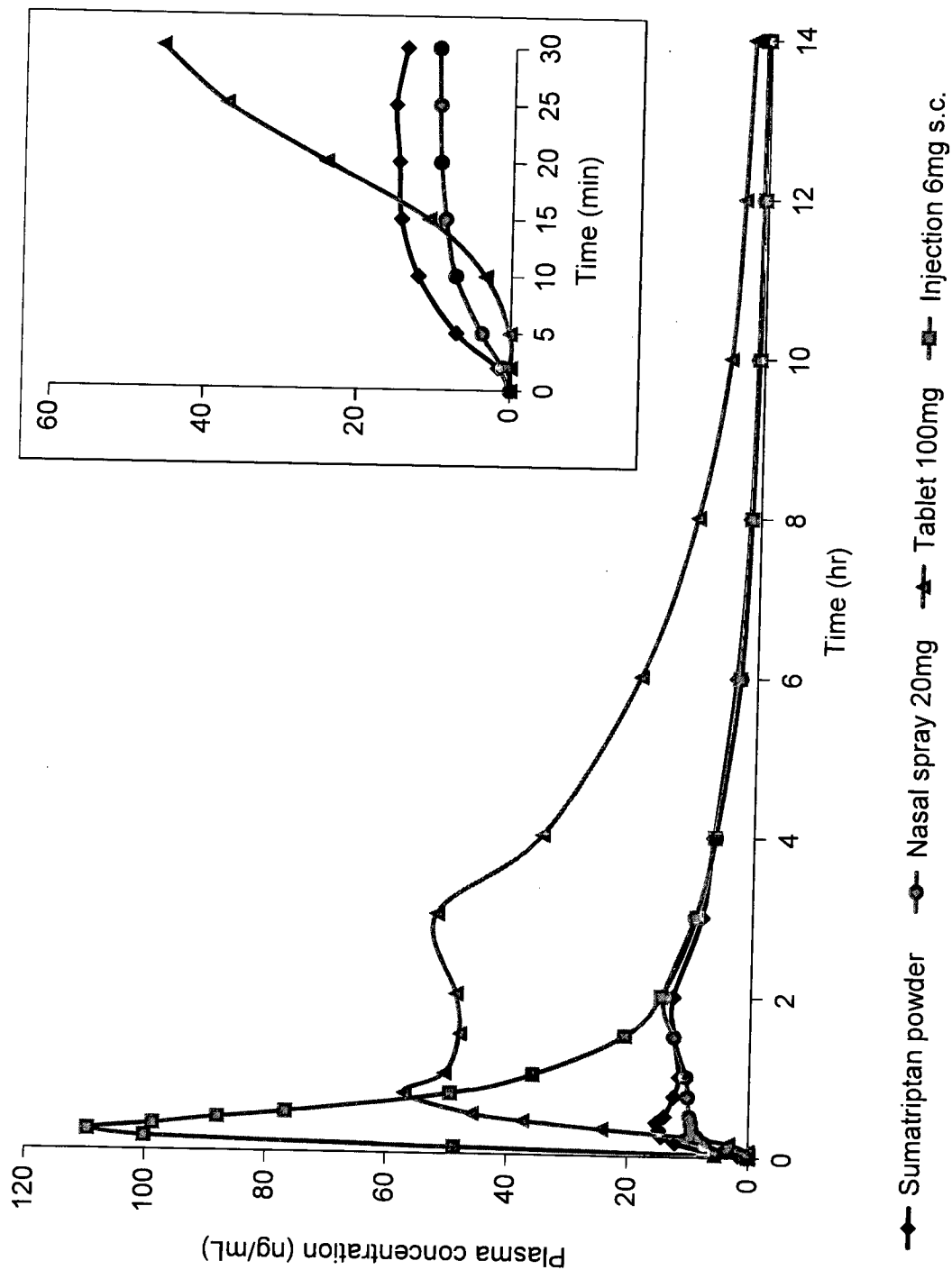


FIG. 6

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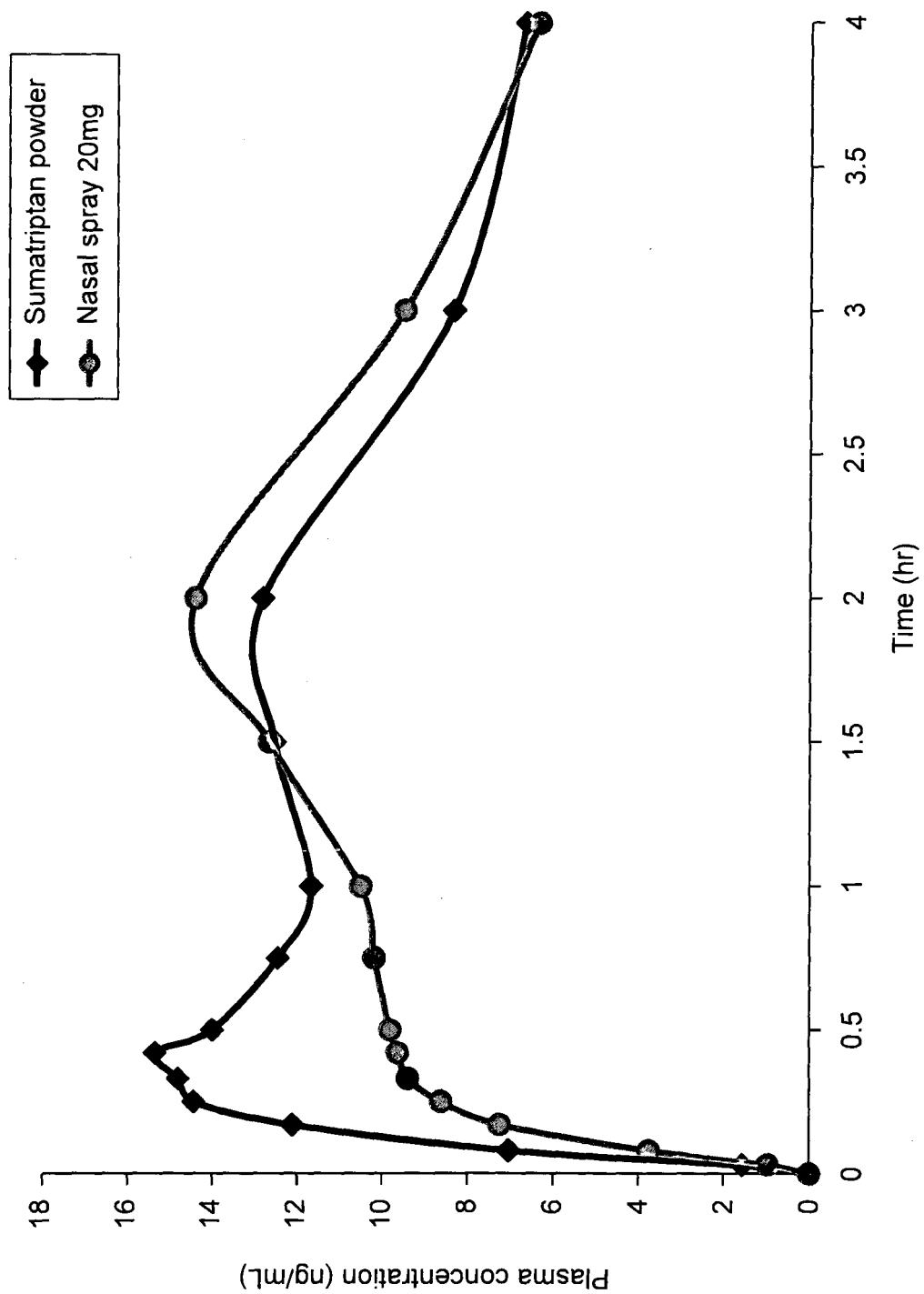


FIG. 7

Sumatriptan Pharmacokinetic Results for Breath Powered Intranasal Delivery of

Sumatriptan Powder Compared with 20 mg Nasal Spray, 100 mg Tablet and 6 mg

Subcutaneous Injection

PK Parameters	Sumatriptan Powder ^a Mean $\pm$ SD (n=20)	20 mg Nasal Spray Mean $\pm$ SD (n=20)	100 mg Oral Tablet Mean $\pm$ SD (n=20)	6 mg S.C. Injection Mean $\pm$ SD (n=20)
C _{max} (ng/mL)	20.8 $\pm$ 12.2	16.4 $\pm$ 5.7	70.2 $\pm$ 25.3	111.6 $\pm$ 21.6
t _{max} (hr) ^b	0.7 (0.2, 2.0)	1.5 (0.2, 2.0)	1.8 (0.5, 3.0)	0.3 (0.2, 0.3)
AUC ₀₋₁ (ng*hr/mL)	63.0 $\pm$ 20.3	59.2 $\pm$ 17.7	292.6 $\pm$ 87.5	127.3 $\pm$ 17.3
AUC _{0-∞} (ng*hr/mL)	64.9 $\pm$ 20.6	61.1 $\pm$ 17.8	308.8 $\pm$ 92.4	128.2 $\pm$ 17.4
AUC _{0-15 min} (ng*hr/mL)	2.1 $\pm$ 1.6	1.2 $\pm$ 0.7	0.7 $\pm$ 0.7	16.2 $\pm$ 4.0
AUC _{0-30 min} (ng*hr/mL)	5.8 $\pm$ 4.1	3.6 $\pm$ 1.9	8.1 $\pm$ 5.0	39.7 $\pm$ 7.1
t _{1/2} (hr)	3.1 $\pm$ 0.6	3.3 $\pm$ 0.9	3.8 $\pm$ 1.8	2.3 $\pm$ 0.4
λ _z	0.2 $\pm$ 0.0	0.2 $\pm$ 0.1	0.2 $\pm$ 0.1	0.3 $\pm$ 0.0
AUC _{%extrap} (%)	3.0 $\pm$ 1.4	3.4 $\pm$ 2.3	5.2 $\pm$ 4.5	0.7 $\pm$ 0.3

^a Sumatriptan powder delivered using the Breath Powered device, mean delivered dose 16 mg.

^b t_{max} is presented as median (minimum, maximum).

SD = standard deviation.

FIG. 8

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Statistical Comparisons of Plasma Sumatriptan Pharmacokinetic Parameters

a) Sumatriptan Powder vs. 20 mg Nasal Spray

Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals	% Intra-subject CV
	Sumatriptan Powder (n=20)	20 mg Nasal Spray (n=20)			
C _{max}	18.4	15.4	119.4	(98.9, 144.1)*	36.7
AUC _{0-t}	60.1	56.5	106.4	(93.8, 120.7)	24.2
AUC _{0-30 min}	4.8	3.1	151.9	(117.1, 197.0)*	52.3
AUC _{0-∞}	61.9	58.4	106.0	(93.6, 120.0)	23.8

b) Sumatriptan Powder vs. 100 mg Oral Tablet

Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals	% Intra-subject CV
	Sumatriptan Powder (n=20)	100 mg Oral Tablets (n=20)			
C _{max}	18.4	66.4	27.7	(23.0, 33.4)*	36.7
AUC _{0-t}	60.1	280.9	21.4	(18.9, 24.3)*	24.2
AUC _{0-30 min}	4.8	6.9	68.5	(52.8, 88.8)*	52.3
AUC _{0-∞}	61.9	296.5	20.9	(18.5, 23.7)*	23.8

c) Sumatriptan Powder vs 6 mg Subcutaneous Injection

Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals	% Intra-subject CV
	Sumatriptan Powder (n=20)	6 mg S.C. Injection (n=20)			
C _{max}	18.4	109.6	16.8	(13.9, 20.2)*	36.7
AUC _{0-t}	60.1	126.2	47.6	(42.0, 54.0)*	24.2
AUC _{0-30 min}	4.8	39.1	12.2	(9.4, 15.8)*	52.3
AUC _{0-∞}	61.9	127.1	48.7	(43.1, 55.2)*	23.8

*Outside the boundary for bioequivalence (entire 90% CI within the range of 80-125%)

Parameters were ln-transformed prior to analysis.

Values for Sumatriptan Powder and 20 mg Nasal Spray are the exponentiated LS means from the ANOVA.

% Geometric Mean Ratio = $100 \cdot \exp(\text{LS mean test} - \text{LS mean reference})$.

% Intra-subject CV = $100 \cdot \sqrt{\exp(s^2) - 1}$, where s^2 is the residual variance component from the ANOVA.

FIG. 9

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Parameter	OptiNose 7.5 mg (Nasal & mixed) GTN – side of migraine	OptiNose 15 mg (7.5 +7.5) (mixed) GTN – split between nostrils	OptiNose 6 mg sc injection GTN challenge	OptiNose 16 mg Nasal Peak	OptiNose 16 mg (mixed)	OptiNose 16 mg GI Peak	Imitrex NS 20 mg Nasal Peak	Imitrex NS 20 mg (mixed)	Imitrex NS 20 mg GI Peak	Optinose 6 mg sc injection
C_{max}	11.0	16.0	96.0	15.2	18.4	13.5	9.7	15.4	14.2	109.6
	20 min	20 min	10 min	15 min	(45 min)	120 min	20 min	(90 min)	120 min	15 min
AUC_{0-t}					60.1			56.5		
$AUC_{0-30 \text{ min}}$					4.8			3.0		
$AUC_{0-\infty}$	37.0	49.0	106.7		61.9			58.4		127.1
Relative BA PK1 GTN Challenge during migraine attack relative BA PK2 healthy volunteers	27.7				18.3			13.8		
	Migraineur	Migraineur	Migraineur	Healthy	Healthy	Healthy	Healthy	Healthy	Healthy	Healthy

FIG. 10

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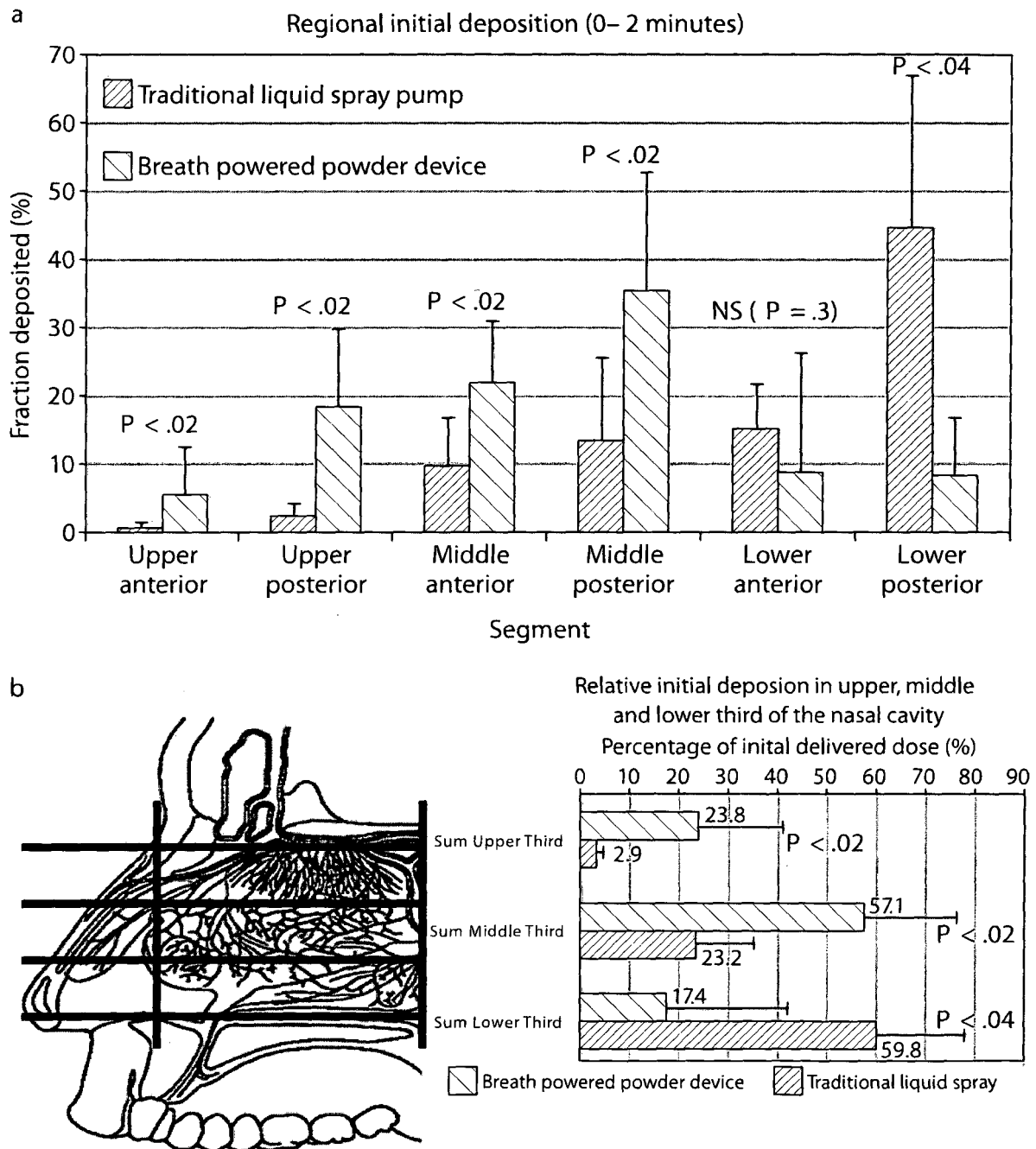


FIG. 11

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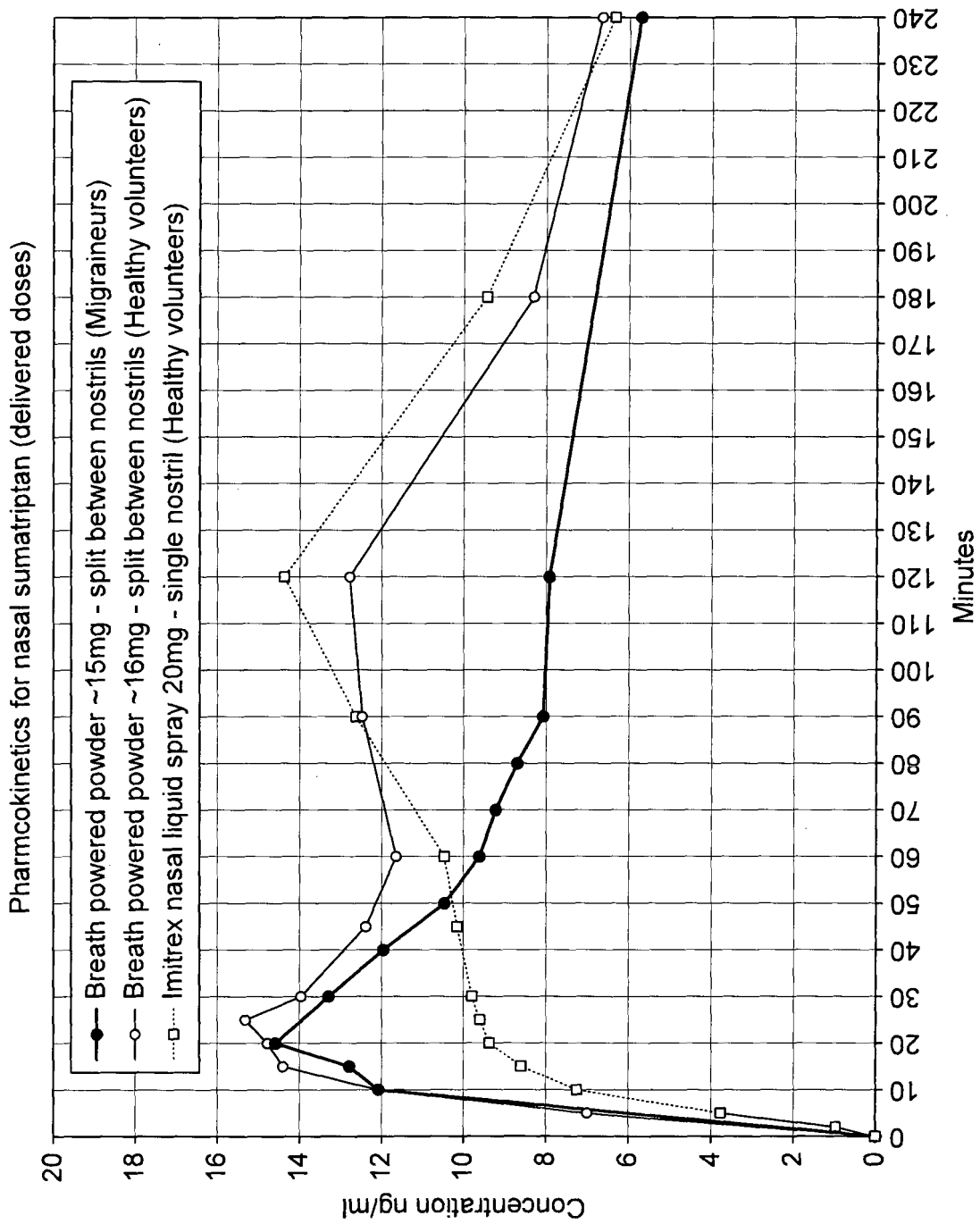


FIG. 12

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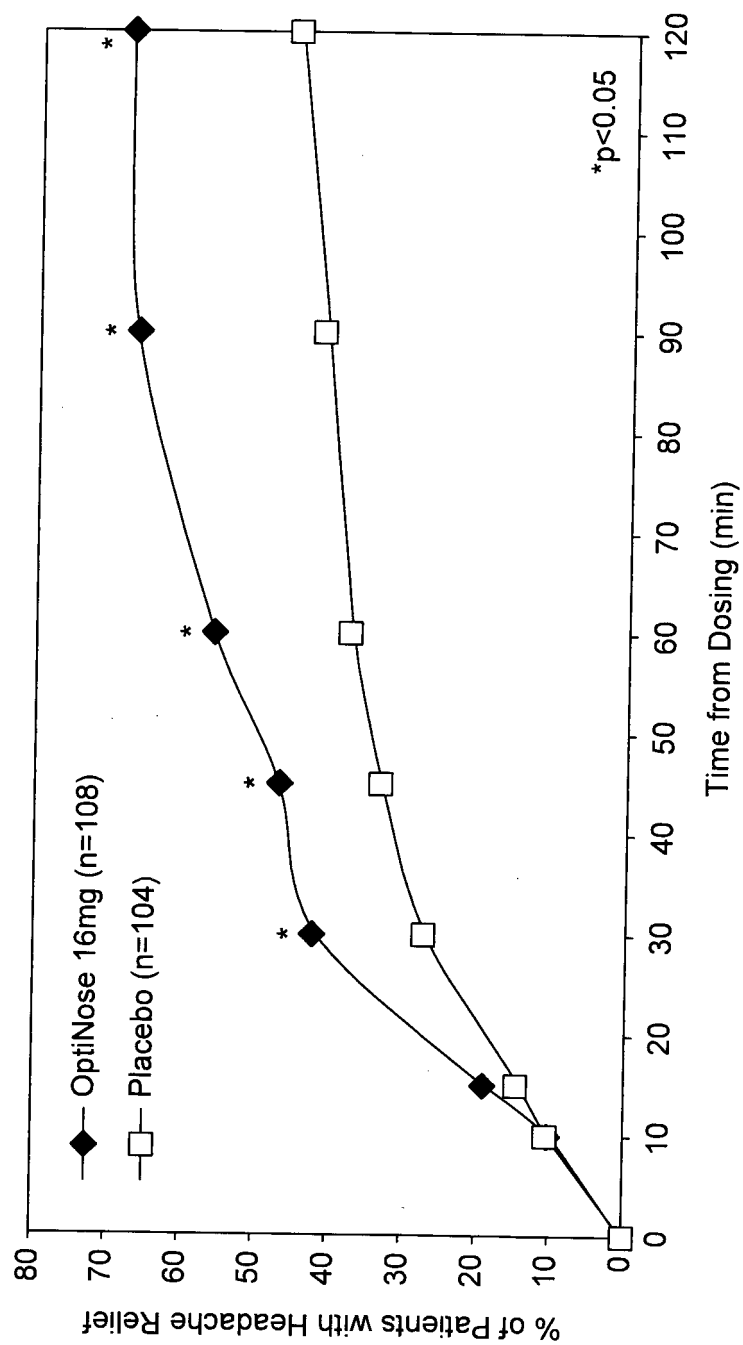


FIG. 13

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Drug (active dose)/study # in package insert	% Active	% Placebo	Therapeutic gain
Sumatriptan (IMITREX, IMIGRAN Tabs) 100 mg Study 1 ¹⁸	62	27	35
Sumatriptan (Suma) Tabs (100 mg) Study 2 ¹⁸	56	26	30
Suma Tabs (100 mg) Study 3 ¹⁸	57	17	40
Suma Injection (6 mg) Study 1 ¹⁹	70	21	49
Suma Injection (6 mg) Study 2 ¹⁹	81	31	50
Suma Injection (6 mg) Study 3 ¹⁹	82	39	43
Suma Nasal Spray (20 mg) Study 1 ²⁰	64	25	19
Suma Nasal Spray (20 mg) Study 2 ²⁰	55	25	30
Suma Nasal Spray (20 mg) Study 3 ²⁰	63	35	28
Suma Nasal Spray (20 mg) Study 4 ²⁰	62	29	33
Suma Nasal Spray (20 mg) Study 5 ²⁰	60	36	24
Eletriptan (RELPAK) (40 mg) Study 1 ²¹	65	24	41
Eletriptan (Ele) (40 mg) Study 2 ²¹	62	19	43
Ele (40 mg) Study 3 ²¹	62	22	40
Ele (40 mg) Study 4 ²¹	62	40	22
Ele (40 mg) Study 5 ²¹	54	21	34
Ele (40 mg) Study 6 ²¹	64	31	33
Ele (40 mg) Study 7 ²¹	58	30	28
Rizatriptan (MAXALT) (10 mg) Study 1 ¹⁶	71	35	36
Rizatriptan (Riza) (10 mg) Study 2 ¹⁶	77	37	40
Riza (10 mg) Study 4 ¹⁶	67	40	27
Riza orally dissolvable tablet (MLT) [ODT] (10 mg) Study 5 ¹⁶	66	47	19
Riza tab ODT 10 mg Study 6 ¹⁶	74	28	46
Frovatriptan (FROVA) (2.5 mg) Study 1 ²²	42	22	20
Frovatriptan (FRV) (2.5 mg) Study 2 ²²	38	25	13
FRV (2.5 mg) Study 3 ²²	39	21	18
FRV (2.5 mg) Study 4 ²²	46	27	19
FRV (2.5 mg) Study 5 ²²	37	23	14
Sumatriptan Naproxen (Treximet) Study 1 ²³	65	28	37
Sumatriptan Naproxen (TRX) Study 2 ²³	57	29	28
Almotriptan (AXERT) (12.5 mg) Study 1 ²⁴	58.5	33.8	24.7
Almotriptan (Almo) (12.5 mg) Study 2 ²⁴	57.1	40.0	17.1
Almo 12.5 mg Study 3 ²⁴	64.9	33.0	31.9
Naratriptan (AMERGE, NARAMIG) 2.5 Study 1 ²⁵	60	34	26
Naratriptan (Nara) (2.5 mg) Study 2 ²⁵	66	27	39
Nara (2.5 mg) Study 3 ²⁵	65	32	33
Zolmitriptan (ZOMIG) Nasal Spray (5 mg) Study 1 ²⁶	69	31	38
Zolmitriptan (Zolmi) Tabs (5 mg) Study 1 ²⁷	60	16	44
Zolmi Tabs (5 mg) Study 2 ²⁷	66	19	47
Zolmi Tabs (5 mg) Study 3 ²⁷	67	34	28
Zolmi Tabs (5 mg) Study 4 ²⁷	59	44	15
Zolmi ODT (ZMT) (2.5 mg) Study 6 ²⁷	63	22	41
Sumatriptan (OPTINOSE) Study 1 ⁹	80	44	36
Breath-powered powder sumatriptan intranasal treatment (BPPSIT) Study 2 ¹⁰	68	45	23

FIG. 14

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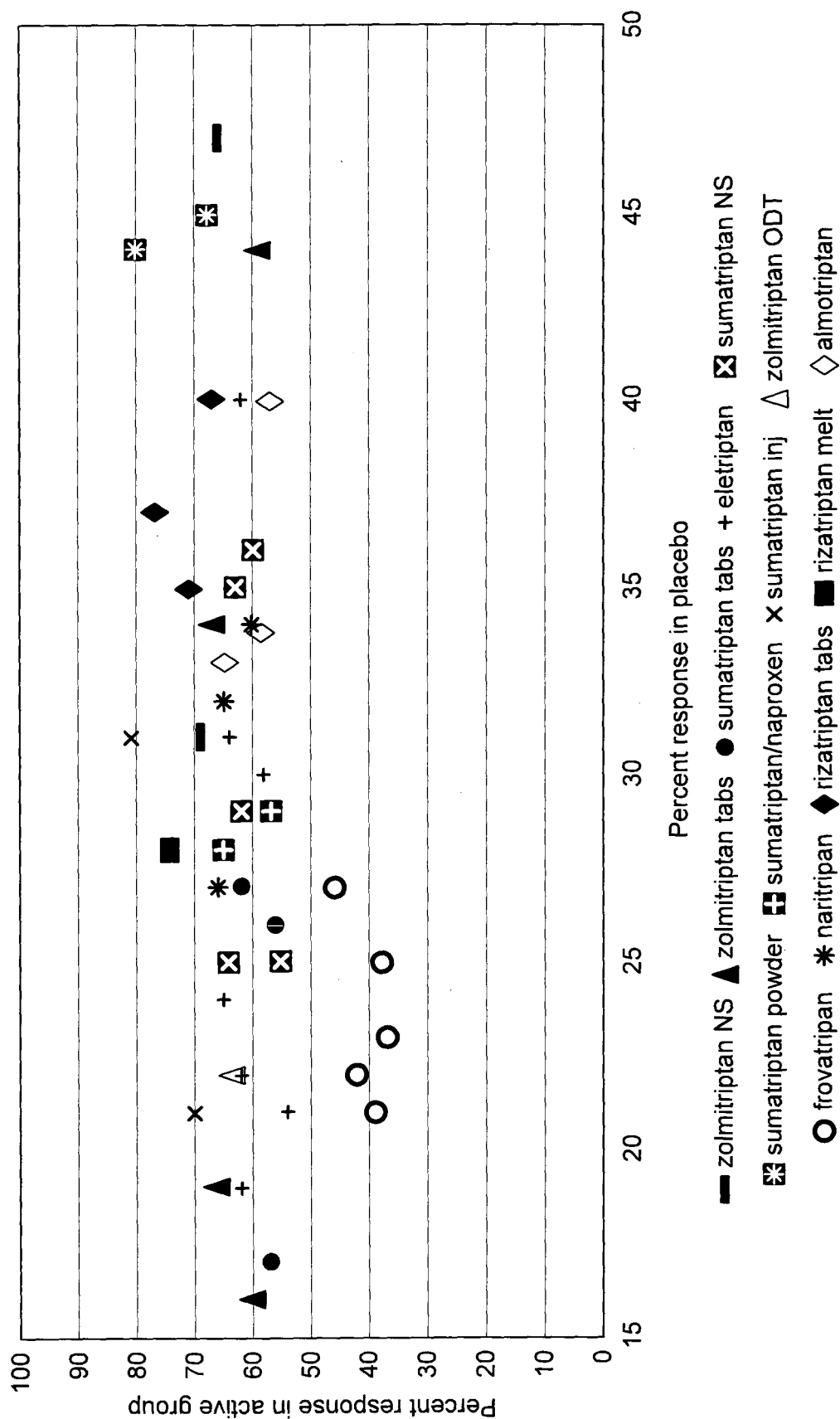


FIG. 15

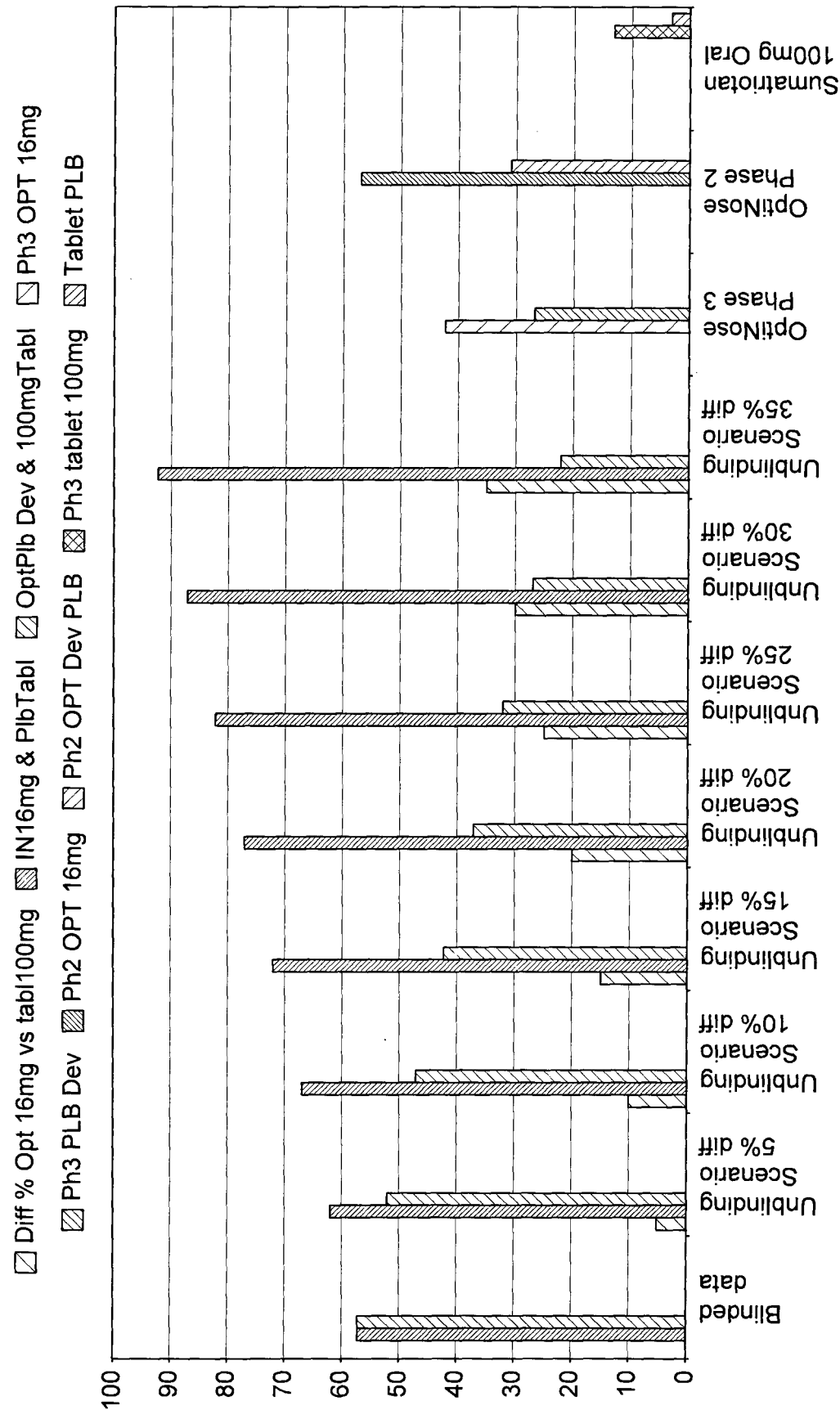


FIG. 16

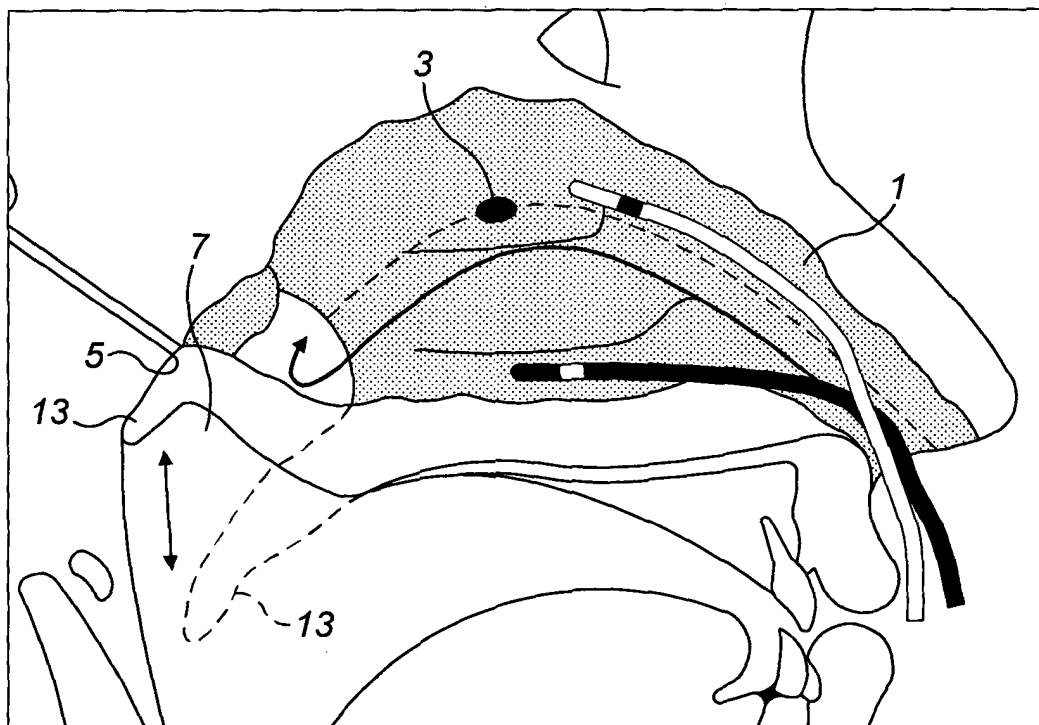


FIG. 17

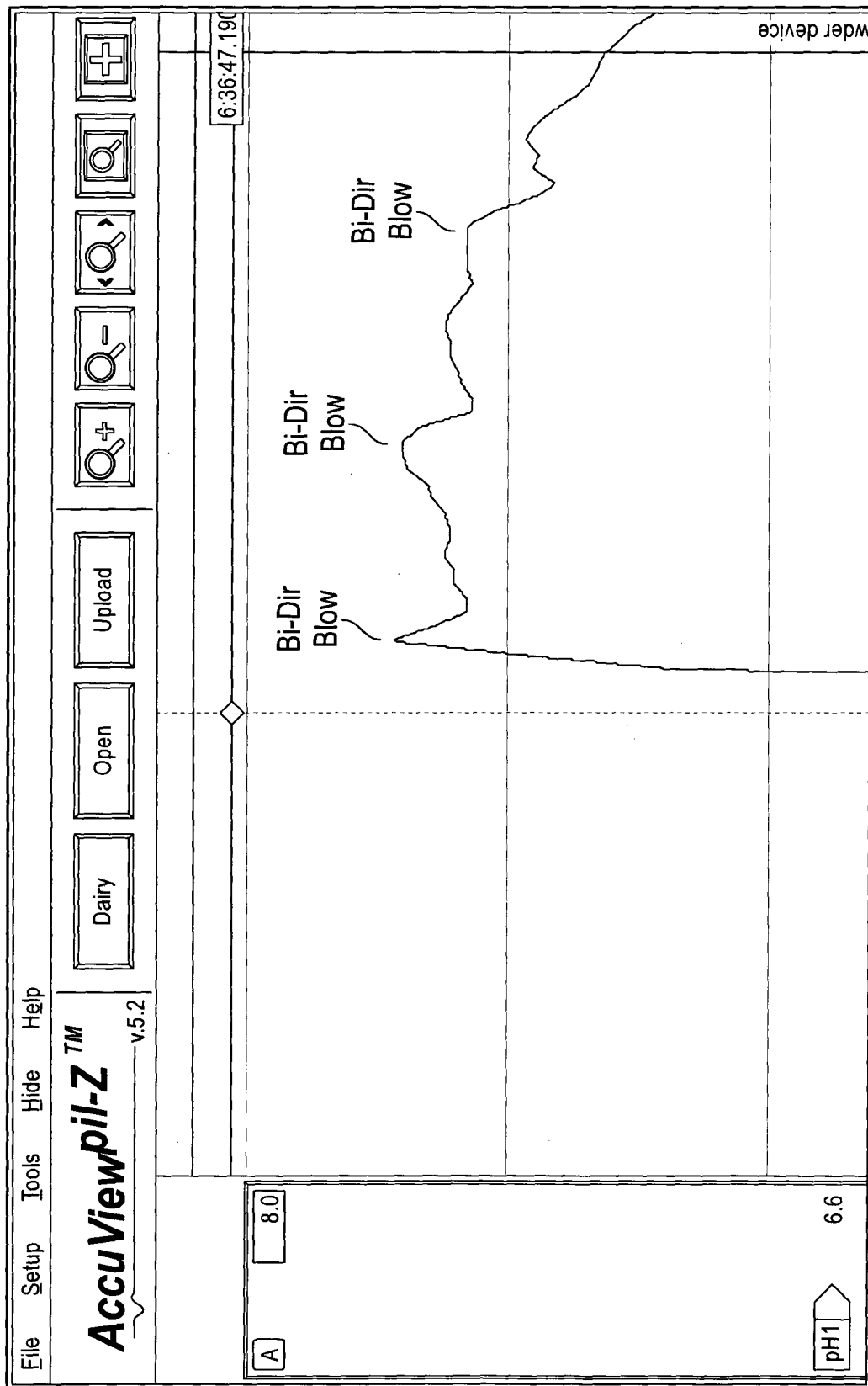


FIG. 18

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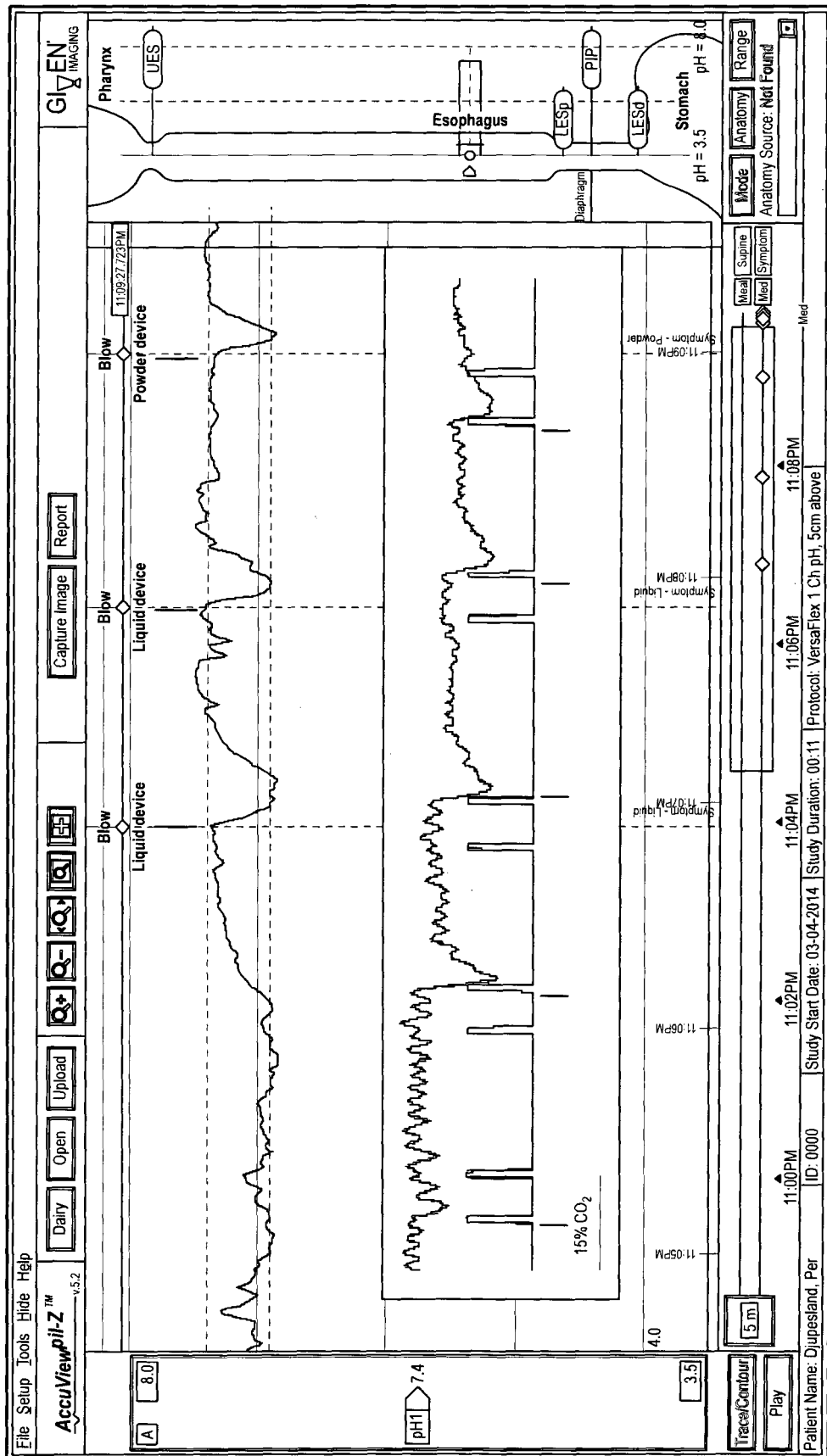


FIG. 19

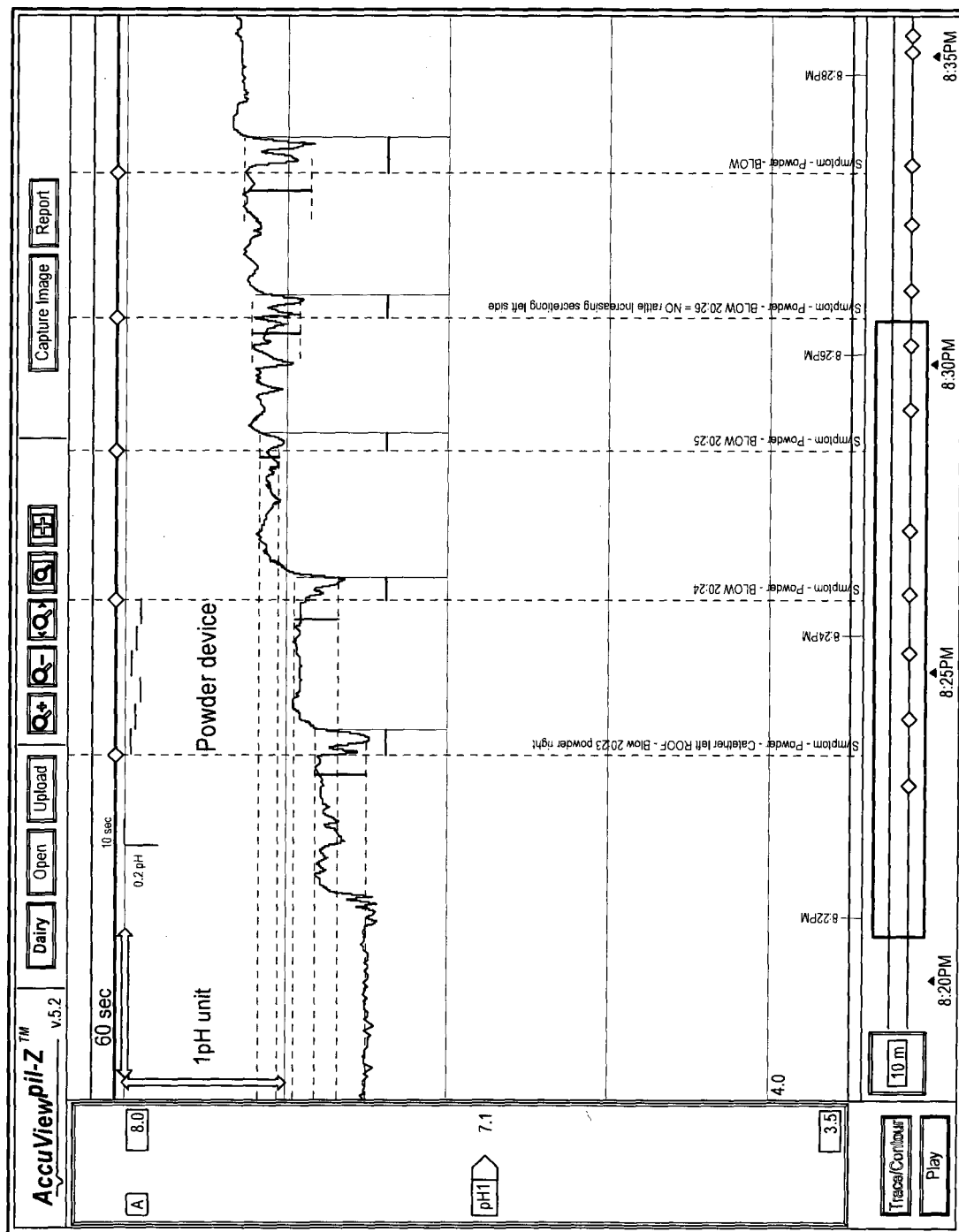


FIG. 20

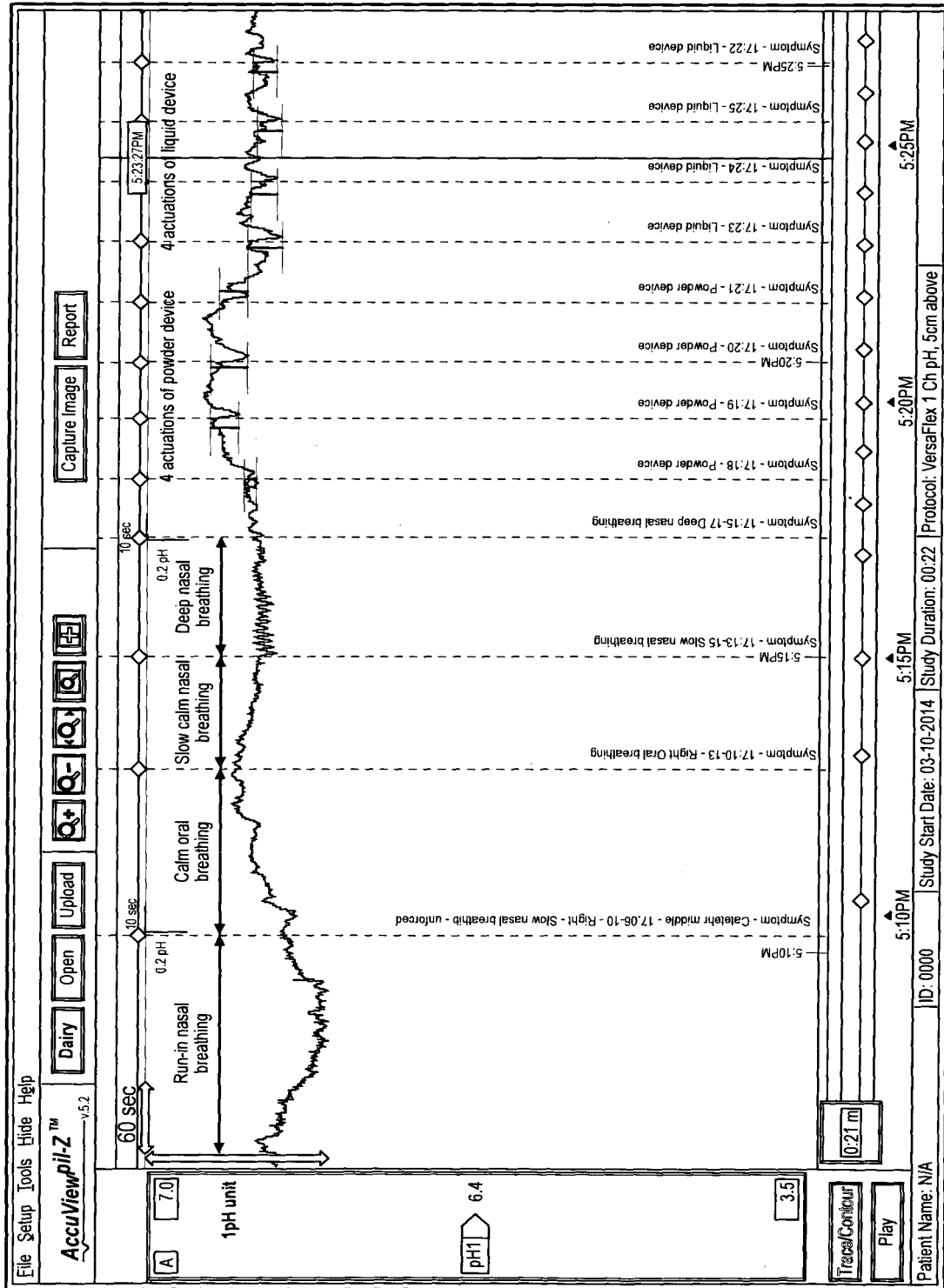
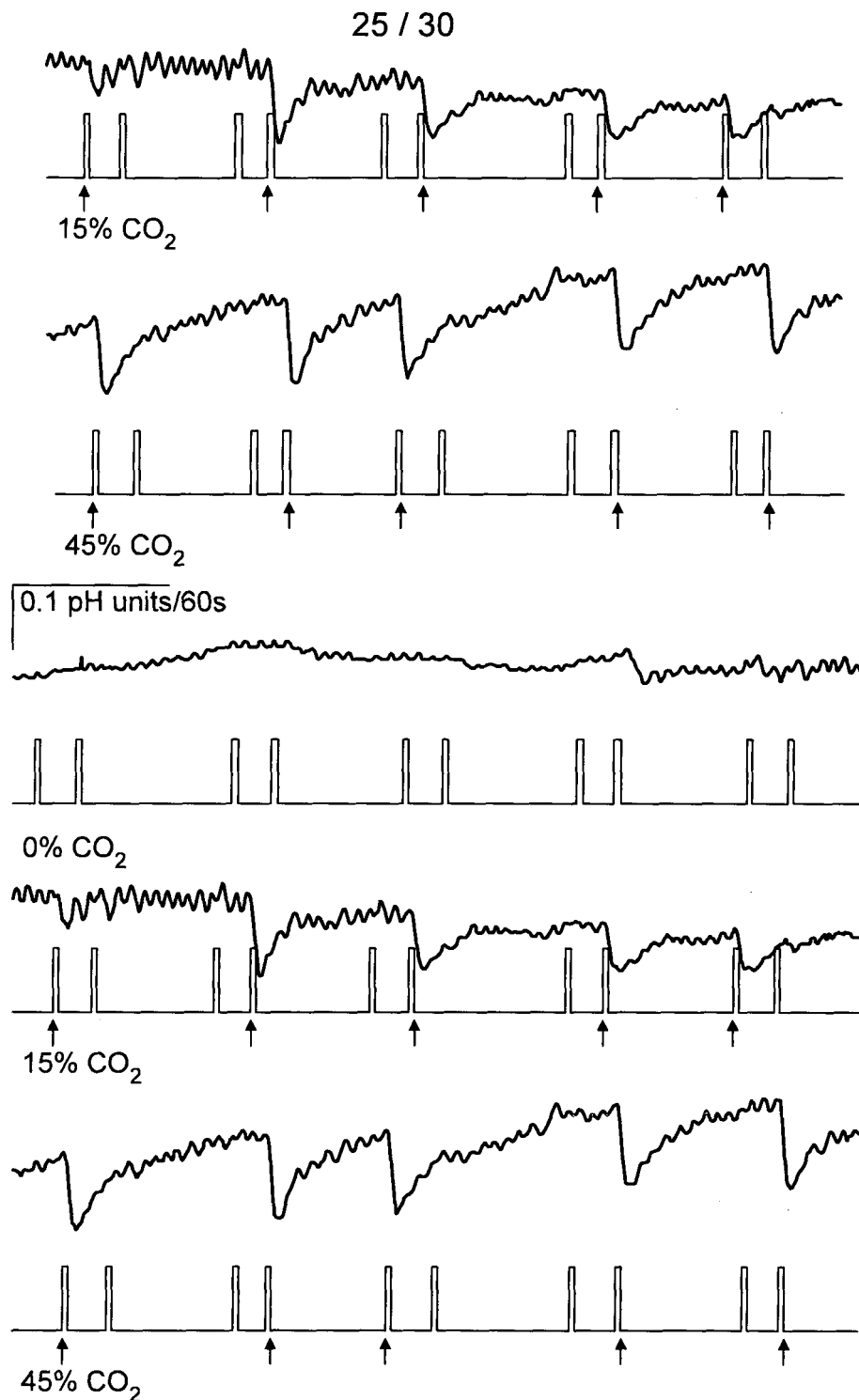


FIG. 21



Example of real-time recording of nasal mucosal pH during pulsed stimulation with CO₂ (rectangular waves with arrows) and air (rectangular waves without arrows). Pulses are 5 l/min., 3.0 s duration, synchronized with inspiration, and delivered dichorhinically by nasal cannula. The first series of pulses were all control (0% CO₂) stimuli; vertical arrows in series 2 and 3 indicate CO₂ stimuli. Note baseline shift (as distinguished from phasic change) during control series (probably due to movement artifact). Subject is a 29 year old female.

FIG. 22
SUBSTITUTE SHEET (RULE 26)

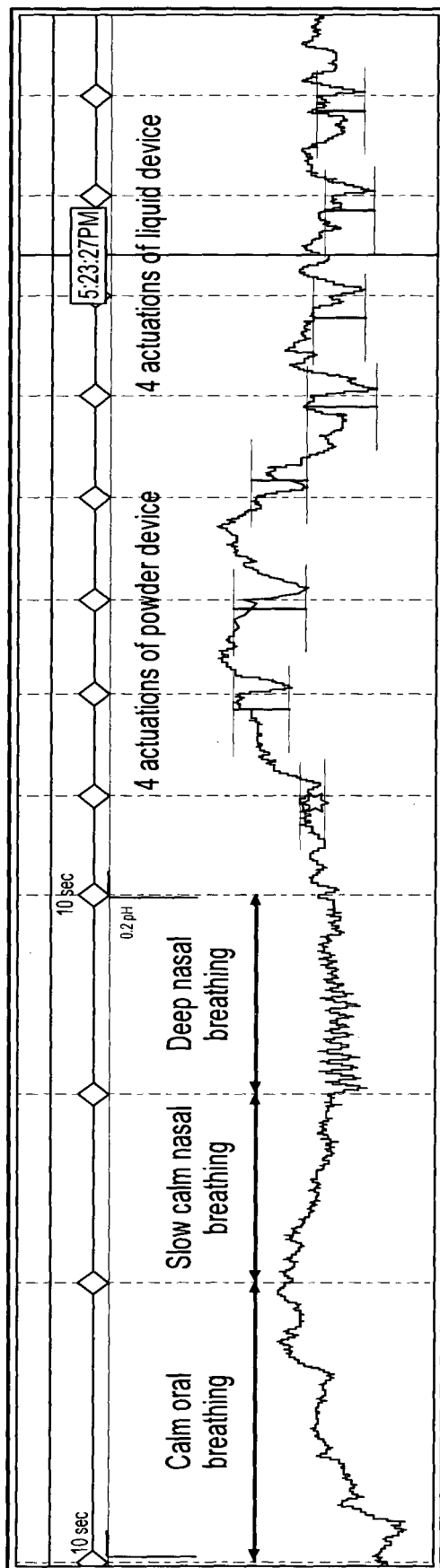


FIG. 23

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Break-Through™

	(AVP-825) 22 mg (n=103)	Placebo device (n=104)	Total (n=212)
Patient Demographics			
Age (years), mean (SD)	41.9 (10.3)	42.0 (10.7)	42.0 (10.5)
Sex, n (%)			
Male	17 (15.7)	18 (17.2)	35 (16.5)
Female	86 (84.3)	86 (82.7)	172 (83.5)
Caucasian race, n (%)	80 (82.3)	82 (81.5)	162 (85.9)
Medical History			
Age at first seizure, mean (SD)	4.5 (1.9)	4.6 (1.8)	4.5 (1.8)
Presence of seizure types			
Partial	20 (19.4)	21 (20.2)	41 (19.3)
Generalized	20 (19.4)	20 (19.3)	40 (18.9)
Partial and generalized	16 (15.5)	16 (15.4)	32 (15.2)
None	17 (16.4)	17 (16.4)	34 (16.0)
Unknown	13 (12.6)	13 (12.5)	26 (12.3)
Duration of seizure-free period, mean (SD)	1.2 (0.8)	1.2 (0.8)	1.2 (0.8)
Duration of seizure-free period, n (%)			
Less than 1 year	10 (9.7)	10 (9.6)	20 (9.4)
1 to 2 years	17 (16.5)	17 (16.3)	34 (15.9)
2 to 3 years	13 (12.6)	13 (12.5)	26 (12.3)
3 to 4 years	10 (9.7)	10 (9.6)	20 (9.4)
4 to 5 years	10 (9.7)	10 (9.6)	20 (9.4)
5 to 6 years	10 (9.7)	10 (9.6)	20 (9.4)
6 to 7 years	10 (9.7)	10 (9.6)	20 (9.4)
7 to 8 years	10 (9.7)	10 (9.6)	20 (9.4)
8 to 9 years	10 (9.7)	10 (9.6)	20 (9.4)
9 to 10 years	10 (9.7)	10 (9.6)	20 (9.4)
10 to 11 years	10 (9.7)	10 (9.6)	20 (9.4)
11 to 12 years	10 (9.7)	10 (9.6)	20 (9.4)
12 to 13 years	10 (9.7)	10 (9.6)	20 (9.4)
13 to 14 years	10 (9.7)	10 (9.6)	20 (9.4)
14 to 15 years	10 (9.7)	10 (9.6)	20 (9.4)
15 to 16 years	10 (9.7)	10 (9.6)	20 (9.4)
16 to 17 years	10 (9.7)	10 (9.6)	20 (9.4)
17 to 18 years	10 (9.7)	10 (9.6)	20 (9.4)
18 to 19 years	10 (9.7)	10 (9.6)	20 (9.4)
19 to 20 years	10 (9.7)	10 (9.6)	20 (9.4)
20 to 21 years	10 (9.7)	10 (9.6)	20 (9.4)
21 to 22 years	10 (9.7)	10 (9.6)	20 (9.4)
22 to 23 years	10 (9.7)	10 (9.6)	20 (9.4)
23 to 24 years	10 (9.7)	10 (9.6)	20 (9.4)
24 to 25 years	10 (9.7)	10 (9.6)	20 (9.4)
25 to 26 years	10 (9.7)	10 (9.6)	20 (9.4)
26 to 27 years	10 (9.7)	10 (9.6)	20 (9.4)
27 to 28 years	10 (9.7)	10 (9.6)	20 (9.4)
28 to 29 years	10 (9.7)	10 (9.6)	20 (9.4)
29 to 30 years	10 (9.7)	10 (9.6)	20 (9.4)
30 to 31 years	10 (9.7)	10 (9.6)	20 (9.4)
31 to 32 years	10 (9.7)	10 (9.6)	20 (9.4)
32 to 33 years	10 (9.7)	10 (9.6)	20 (9.4)
33 to 34 years	10 (9.7)	10 (9.6)	20 (9.4)
34 to 35 years	10 (9.7)	10 (9.6)	20 (9.4)
35 to 36 years	10 (9.7)	10 (9.6)	20 (9.4)
36 to 37 years	10 (9.7)	10 (9.6)	20 (9.4)
37 to 38 years	10 (9.7)	10 (9.6)	20 (9.4)
38 to 39 years	10 (9.7)	10 (9.6)	20 (9.4)
39 to 40 years	10 (9.7)	10 (9.6)	20 (9.4)
40 to 41 years	10 (9.7)	10 (9.6)	20 (9.4)
41 to 42 years	10 (9.7)	10 (9.6)	20 (9.4)
42 to 43 years	10 (9.7)	10 (9.6)	20 (9.4)
43 to 44 years	10 (9.7)	10 (9.6)	20 (9.4)
44 to 45 years	10 (9.7)	10 (9.6)	20 (9.4)
45 to 46 years	10 (9.7)	10 (9.6)	20 (9.4)
46 to 47 years	10 (9.7)	10 (9.6)	20 (9.4)
47 to 48 years	10 (9.7)	10 (9.6)	20 (9.4)
48 to 49 years	10 (9.7)	10 (9.6)	20 (9.4)
49 to 50 years	10 (9.7)	10 (9.6)	20 (9.4)
50 to 51 years	10 (9.7)	10 (9.6)	20 (9.4)
51 to 52 years	10 (9.7)	10 (9.6)	20 (9.4)
52 to 53 years	10 (9.7)	10 (9.6)	20 (9.4)
53 to 54 years	10 (9.7)	10 (9.6)	20 (9.4)
54 to 55 years	10 (9.7)	10 (9.6)	20 (9.4)
55 to 56 years	10 (9.7)	10 (9.6)	20 (9.4)
56 to 57 years	10 (9.7)	10 (9.6)	20 (9.4)
57 to 58 years	10 (9.7)	10 (9.6)	20 (9.4)
58 to 59 years	10 (9.7)	10 (9.6)	20 (9.4)
59 to 60 years	10 (9.7)	10 (9.6)	20 (9.4)
60 to 61 years	10 (9.7)	10 (9.6)	20 (9.4)
61 to 62 years	10 (9.7)	10 (9.6)	20 (9.4)
62 to 63 years	10 (9.7)	10 (9.6)	20 (9.4)
63 to 64 years	10 (9.7)	10 (9.6)	20 (9.4)
64 to 65 years	10 (9.7)	10 (9.6)	20 (9.4)
65 to 66 years	10 (9.7)	10 (9.6)	20 (9.4)
66 to 67 years	10 (9.7)	10 (9.6)	20 (9.4)
67 to 68 years	10 (9.7)	10 (9.6)	20 (9.4)
68 to 69 years	10 (9.7)	10 (9.6)	20 (9.4)
69 to 70 years	10 (9.7)	10 (9.6)	20 (9.4)
70 to 71 years	10 (9.7)	10 (9.6)	20 (9.4)
71 to 72 years	10 (9.7)	10 (9.6)	20 (9.4)
72 to 73 years	10 (9.7)	10 (9.6)	20 (9.4)
73 to 74 years	10 (9.7)	10 (9.6)	20 (9.4)
74 to 75 years	10 (9.7)	10 (9.6)	20 (9.4)
75 to 76 years	10 (9.7)	10 (9.6)	20 (9.4)
76 to 77 years	10 (9.7)	10 (9.6)	20 (9.4)
77 to 78 years	10 (9.7)	10 (9.6)	20 (9.4)
78 to 79 years	10 (9.7)	10 (9.6)	20 (9.4)
79 to 80 years	10 (9.7)	10 (9.6)	20 (9.4)
80 to 81 years	10 (9.7)	10 (9.6)	20 (9.4)
81 to 82 years	10 (9.7)	10 (9.6)	20 (9.4)
82 to 83 years	10 (9.7)	10 (9.6)	20 (9.4)
83 to 84 years	10 (9.7)	10 (9.6)	20 (9.4)
84 to 85 years	10 (9.7)	10 (9.6)	20 (9.4)
85 to 86 years	10 (9.7)	10 (9.6)	20 (9.4)
86 to 87 years	10 (9.7)	10 (9.6)	20 (9.4)
87 to 88 years	10 (9.7)	10 (9.6)	20 (9.4)
88 to 89 years	10 (9.7)	10 (9.6)	20 (9.4)
89 to 90 years	10 (9.7)	10 (9.6)	20 (9.4)
90 to 91 years	10 (9.7)	10 (9.6)	20 (9.4)
91 to 92 years	10 (9.7)	10 (9.6)	20 (9.4)
92 to 93 years	10 (9.7)	10 (9.6)	20 (9.4)
93 to 94 years	10 (9.7)	10 (9.6)	20 (9.4)
94 to 95 years	10 (9.7)	10 (9.6)	20 (9.4)
95 to 96 years	10 (9.7)	10 (9.6)	20 (9.4)
96 to 97 years	10 (9.7)	10 (9.6)	20 (9.4)
97 to 98 years	10 (9.7)	10 (9.6)	20 (9.4)
98 to 99 years	10 (9.7)	10 (9.6)	20 (9.4)
99 to 100 years	10 (9.7)	10 (9.6)	20 (9.4)

Fig. 24

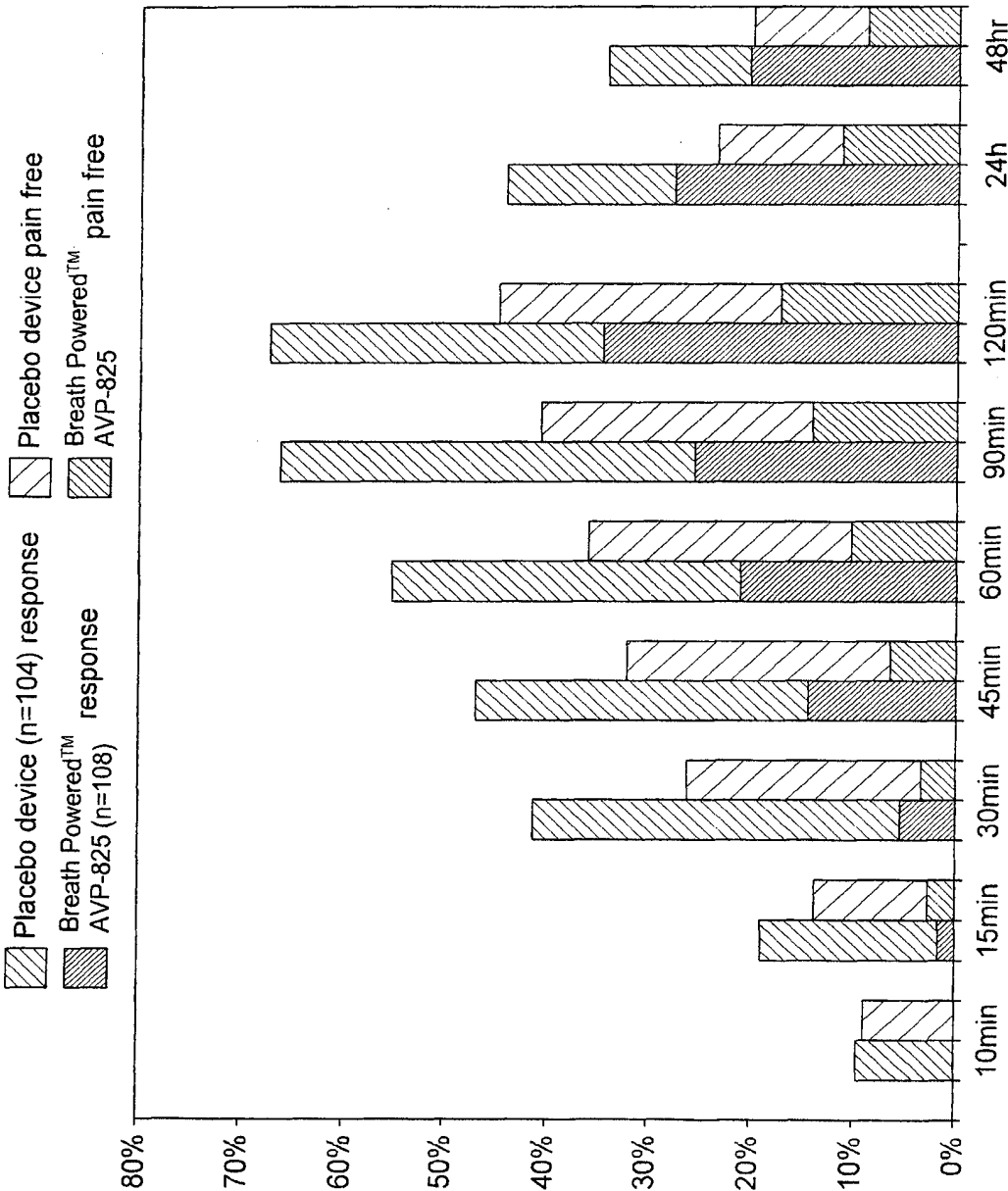
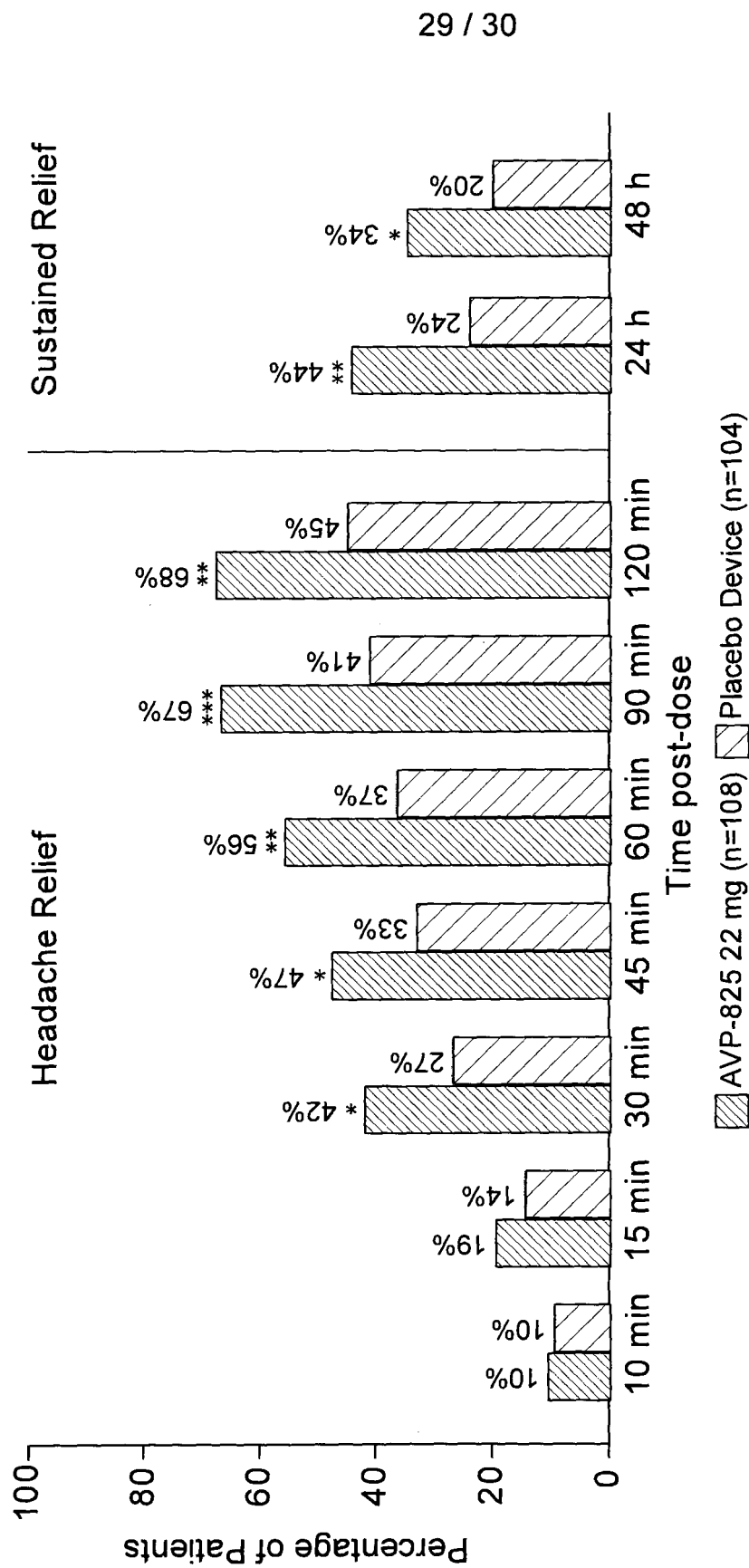


FIG. 25

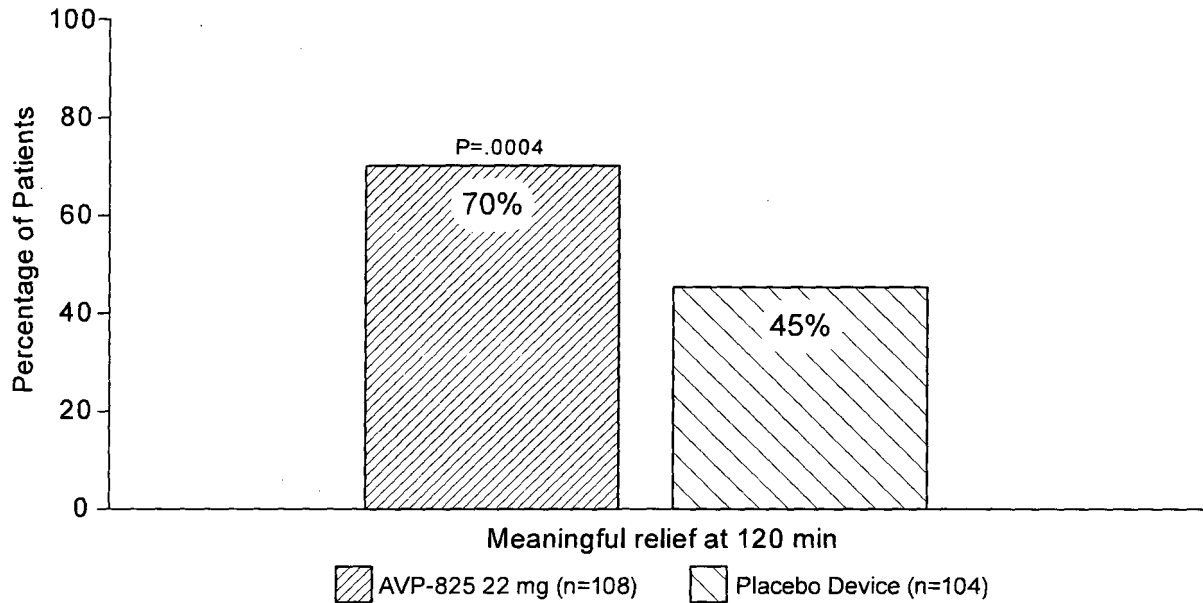


^aHeadache relief=reduction from severe (Grade 3) or moderate (Grade 2) headache pain to mild (Grade 1) headache pain or none (Grade 0).
^bSustained relief at 24 or 48 h was calculated for patients with headache relief at 120 min and required that patients had no recurrence of headache, or rescue medication usage during that timeframe.

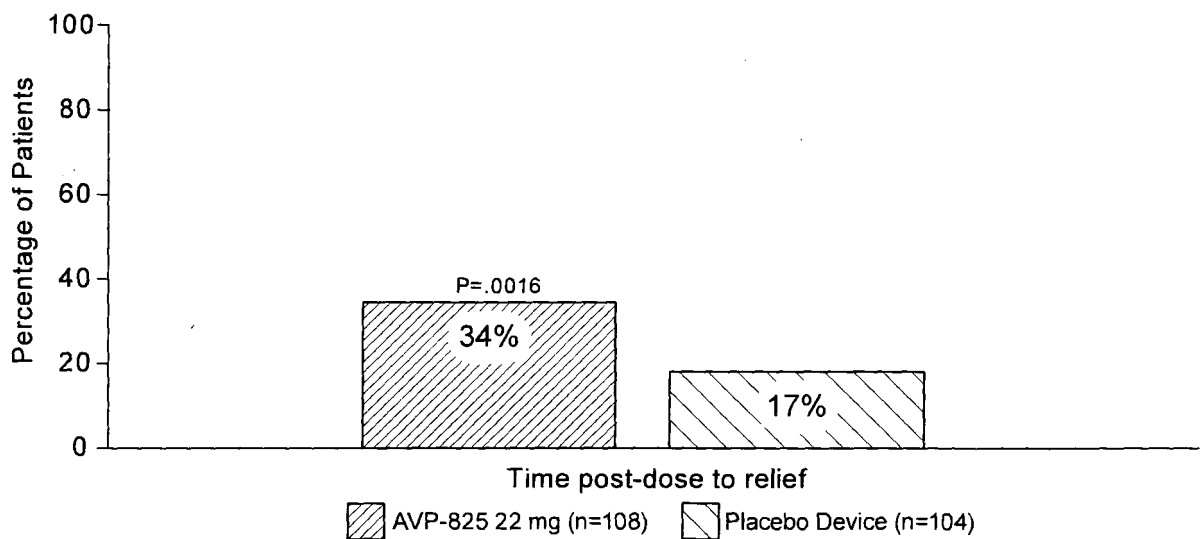
*P<.05; **P<.01; ***P<.001.

FIG. 26

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^aMeaningful relief=patient reported interpretation of headache pain relief.

FIG. 27

^aPain Freedom=freedom from headache pain, defined as a reduction from severe (Grade 3) or moderate (Grade 2) headache pain to none (Grade 0).

FIG. 28